Marc C. Sanchez, Esq.
Contract In-House Counsel and Consultants, LLC
53516 Bickett
Chapel Hill NC 27517

RE: Petition for a Qualified Health Claim for Ground Peanuts and Reduced Risk of Developing Peanut Allergy (Docket No. FDA-2016-Q-0274)

Dear Mr. Sanchez,

This letter responds to the qualified health claim petition received by the Food and Drug Administration (FDA or the agency) on December 16, 2015, that you submitted on behalf of Assured Bites, Inc., pursuant to section 403(r)(4) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 343(r)(4)).[1,2] The petition requested that the agency exercise enforcement discretion for a qualified health claim "characterizing the relationship between the consumption of peanut flour (ground whole peanuts) by children aged four (4) months and older and the reduced risk of developing peanut allergies."[3]

The petition proposed the following model health claims to be used on the labels or in the labeling of "peanut flour (ground whole peanuts)":

- Emerging clinical research suggests the early introduction of peanuts to infants aged 4 to 60 months may reduce the likelihood of children developing an allergic reaction to peanuts; or

- An initial clinical study suggests the early introduction of peanuts to infants aged 4 to 60 months may be linked to a reduced likelihood of developing an allergic reaction to peanuts; or

- Research shows the early introduction of peanuts to infants ready for solid foods may reduce the likelihood of developing an allergic reaction to peanuts later in life.

FDA filed the petition on January 29, 2016, and posted the petition on the FDA website for a 60-day comment period, consistent with FDA's guidance on the procedures for the submission of

[1] The agency notes that the petition was submitted pursuant to 21 U.S.C. 343(r)(4) and 343(r)(5)(D) (petition, page 2). The latter statutory provision is inapplicable because the "substance is to be consumed as part of conventional foods" (petition, page 3).
[2] See FDA, "Consumer Health Information for Better Nutrition Initiative: Task Force Final Report," July 10, 2003 [http://www.fda.gov/Food/IngredientsPackagingLabeling/LabelingNutrition/ucm096010.htm].
[3] Petition, page 3.

qualified health claim petitions.[4] The date for the agency's response to the petition was extended to September 6, 2017, by mutual agreement. There were no comments submitted to the docket for this petition.

This letter sets forth the results of FDA's review of the scientific evidence for the qualified health claims requested in the petition. As explained in this letter, FDA has determined that the current scientific evidence supports a qualified health claim in the labeling of conventional foods that contain ground peanuts concerning the relationship between ground peanuts and a reduced risk of developing peanut allergy for a specific population of infants and children over a specific period of time. Accordingly, this letter discusses the factors that FDA intends to consider in the exercise of its enforcement discretion for a qualified health claim for conventional foods, with respect to consumption of foods containing ground peanuts and reduced risk of developing peanut allergy.

I. Overview of Data and Eligibility for a Qualified Health Claim

A health claim characterizes the relationship between a substance and a disease or health-related condition (21 CFR 101.14(a)(1)). The substance must be associated with a disease or health-related condition for which the general United States (U.S.) population, or an identified U.S. population subgroup is at risk (21 CFR 101.14(b)(1)). Health claims characterize the relationship between the substance and a reduction in risk of contracting a particular disease or health-related condition.[5] In a review of a qualified health claim, the agency first identifies the substance and disease or health-related condition that is the subject of the proposed claim and the population to which the claim is targeted.[6]

FDA considers the data and information provided in the petition, in addition to other written data and information available to the agency, to determine whether the data and information could support a relationship between the substance and the disease or health-related condition.[7] The agency then separates individual reports of human studies from other types of data and information. FDA focuses its review on reports of human intervention and observational studies.[8]

---

[4] See FDA, "Interim Procedures for Qualified Health Claims in the Labeling of Conventional Human Food and Human Dietary Supplements," July 10, 2003 [http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm053832.htm].

[5] See *Whitaker v. Thompson*, 353 F.3d 947, 950-51 (D.C. Cir.) (upholding FDA's interpretation of what constitutes a health claim), *cert. denied*, 125 S. Ct. 310 (2004).

[6] See FDA, "Guidance for Industry: Evidence-Based Review System for the Scientific Evaluation of Health Claims - Final," January 2009 ("guidance on scientific evaluation of health claims") [http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/LabelingNutrition/ucm073332.htm].

[7] For brevity, "disease" will be used as shorthand for "disease or health-related condition" in the rest of this letter except when quoting or paraphrasing a regulation that uses the longer term.

[8] In an intervention study, subjects similar to each other are randomly assigned to either receive the intervention or not to receive the intervention, whereas in an observational study, the subjects (or their medical records) are observed for a certain outcome (i.e., disease). Intervention studies provide the strongest evidence for an effect. See *supra*, note 6 [Section III.B, "Intervention Studies"].

In addition to individual reports of human studies, the agency also considers other types of data and information in its review, such as meta-analyses,[9] review articles,[10] and animal and *in vitro* studies. These other types of data and information may be useful to assist the agency in understanding the scientific issues about the substance, the disease, or both, but cannot by themselves support a health claim relationship. Reports that discuss a number of different studies, such as meta-analyses and review articles, do not provide sufficient information on the individual studies reviewed for FDA to determine critical elements such as the study population characteristics and the composition of the products used. Similarly, the lack of detailed information on studies summarized in review articles and meta-analyses prevents FDA from determining whether the studies are flawed in critical elements such as design, conduct of studies, and data analysis. FDA must be able to review the critical elements of a study to determine whether any scientific conclusions can be drawn from it. Therefore, FDA uses meta-analyses, review articles, and similar publications[11] to identify reports of additional studies that may be useful to the health claim review and as background about the substance-disease relationship.[12] If additional studies are identified, the agency evaluates them individually.

FDA uses animal and *in vitro* studies as background information regarding mechanisms of action that might be involved in any relationship between the substance and the disease. The physiology of animals is different than that of humans. *In vitro* studies are conducted in an artificial environment and cannot account for a multitude of normal physiological processes such as digestion, absorption, distribution, and metabolism that affect how humans respond to the consumption of foods and dietary substances (Institute of Medicine (IOM), 2005). Animal and *in vitro* studies can be used to generate hypotheses or to explore a mechanism of action but cannot adequately support a relationship between the substance and the disease.

FDA evaluates the individual reports of human studies to determine whether any scientific conclusions can be drawn from each study. The absence of critical factors such as a control group or a statistical analysis means that scientific conclusions cannot be drawn from the study (Spilker, 1991; Federal Judicial Center, 2000). Studies from which FDA cannot draw any scientific conclusions do not support the health claim relationship, and these are eliminated from further review.

Because health claims involve reducing the risk of a disease in people who do not already have the disease that is the subject of the claim, FDA considers evidence from studies in individuals diagnosed with the disease that is the subject of the health claim only if it is scientifically appropriate to extrapolate to individuals who do not have the disease. That is, the available scientific evidence must demonstrate that: (1) the mechanism(s) for the mitigation or treatment effects measured in the diseased populations are the same as the mechanism(s) for risk reduction

---

[9] A meta-analysis is the process of systematically combining and evaluating the results of clinical trials that have been completed or terminated (Spilker, 1991).

[10] Review articles summarize the findings of individual studies.

[11] Other examples include book chapters, abstracts, letters to the editor, and committee reports.

[12] Although FDA does not generally use meta-analyses in its health claim evaluations for the reasons discussed in the text, the agency will include a meta-analysis in its scientific evaluation if the meta-analysis was conducted with pooled data from all the publicly available studies from which scientific conclusions can be drawn (based on the criteria in FDA's guidance on scientific evaluation of health claims) and the statistical analyses were properly conducted. See *supra*, note 6 [Section III.B, "Research Synthesis Studies"].

effects in non-diseased populations; and (2) the substance affects these mechanisms in the same way in both diseased people and healthy people. If such evidence is not available, the agency cannot draw any scientific conclusions from studies that use diseased subjects to evaluate the substance-disease relationship.

Next, FDA rates the remaining human intervention and observational studies for methodological quality. This quality rating is based on several criteria related to study design (e.g., use of a placebo control versus a non-placebo controlled group), data collection (e.g., type of dietary assessment method), the quality of the statistical analysis, the type of outcome measured (e.g., disease incidence versus validated surrogate endpoint), and study population characteristics other than relevance to the U.S. population (e.g., selection bias and whether important information about the study subjects – e.g., age, smoker vs. non-smoker – was gathered and reported). For example, if the scientific study adequately addressed all or most of the above criteria, it would receive a high methodological quality rating. Moderate or low quality ratings would be given based on the extent of the deficiencies or uncertainties in the quality criteria.

Studies that are so deficient that scientific conclusions cannot be drawn from them cannot be used to support the health claim relationship, and these are eliminated from further review.

Finally, FDA evaluates the results of the remaining studies. The agency then rates the strength of the total body of publicly available evidence.[13] The agency conducts this rating evaluation by considering the study type (e.g., intervention, prospective cohort, case-control, cross-sectional), the methodological quality rating previously assigned, the quantity of evidence (number of the various types of studies and sample sizes), whether the body of scientific evidence supports a health claim relationship for the U.S. population or target subgroup, whether study results supporting the proposed claim have been replicated,[14] and the overall consistency[15] of the total body of evidence.[16] Based on the totality of the scientific evidence, FDA determines whether such evidence is credible to support a qualified health claim for the substance/disease relationship, and, if so considers what qualifying language should be included to convey the limits on the level of scientific evidence supporting the relationship and to prevent the claim from being misleading in other ways.

A. Substance

A health claim characterizes the relationship between a substance and a disease or health-related condition (21 CFR 101.14(a)(1)). A substance means a specific food or component of food (21 CFR 101.14(a)(2)). The petition identified "ground whole peanuts" and "peanut flour" as interchangeable terms to describe the substance that is the subject of the proposed claim. For the purpose of this health claim, we consider "ground peanuts" to adequately describe the substance.

---

[13] See *supra*, note 6 [Section III.F].
[14] Replication of scientific findings is important for evaluating the strength of scientific evidence (Wilson, 1990).
[15] Consistency of findings among similar and different study designs is important for evaluating causation and the strength of scientific evidence (Hill, A.B. The environment and disease: association or causation? Proc R Soc Med 1965;58:295-300); See also, Agency for Healthcare Research and Quality, "Systems to rate the scientific evidence" (March 2002) [http://archive.ahrq.gov/clinic/epcsums/strengthsum.pdf], defining "consistency" as "the extent to which similar findings are reported using similar and different study designs."
[16] See *supra*, note 6 [Section III.F].

We use the terms "peanut" or "peanuts" interchangeably in this letter with "ground peanuts," and each word refers to the substance of the claim, "ground peanuts." For purposes of this qualified health claim, we describe the substance as "foods containing ground peanuts." The petitioner listed a number of age-appropriate foods in its petition to which ground peanuts may be added as an ingredient (e.g., baby cereal, applesauce and yogurt).

Ground peanuts are made from whole peanuts that have been physically changed to a different form and do not include whole or chopped peanuts. The physical form of the substance is important for this health claim. This claim is directed to a population as young as four months old and up to 60 months old (or 5 years of age). The NIH NIAID Addendum Guidelines for the Prevention of Peanut Allergy in the United States, [17] hereinafter referred to as the NIAID Addendum Guidelines, warn that consuming whole nuts poses a choking risk to children under five years of age. Therefore, foods that bear this claim should not contain whole peanuts, alone or in combination with other forms of peanuts. We also note that, consistent with the NIAID Addendum Guidelines, peanut butter should not be fed directly from a spoon or in lumps to children less than four years of age.[18]

Peanuts, along with foods such as beans and peas, belong to the plant family, *Leguminosae*. Legumes are edible seeds enclosed in pods.[19] A peanut is an article used for food and, therefore, meets the definition of food under the Act (21 U.S.C. 321(f)(1)). Peanuts in ground form are also food under 21 U.S.C. 321(f)(1). Moreover, ground peanuts are food within the meaning of 21 U.S.C. 321(f)(3) when used as a component of food. The agency concludes that ground peanuts meet the definition of substance in the health claim regulation (21 CFR 101.14(a)(2)), as they are a specific food or a component of food.

B. Disease or Health-Related Condition

A disease or health-related condition means damage to an organ, part, structure, or system of the body such that it does not function properly or a state of health leading to such dysfunctioning (21 CFR 101.14(a)(5)). The petition has identified peanut allergy as the disease or health-related condition for the proposed claim. Peanut allergy, a type of food allergy, encompasses a group of disorders arising from a specific immune response that occurs reproducibly on exposure to peanut and/or peanut protein.[20] Self-reported peanut allergy was estimated to affect 0.4% of children and 0.7% of adults in the U.S.in 1997,[21] and by 2008, peanut allergy prevalence had increased to approximately 1.4% among children (Sicherer et al., 2010). Other recent population

---

[17] National Institute of Allergy and Infectious Diseases, "Addendum Guidelines for the Prevention of Peanut Allergy in the United States: Report of the National Institute of Allergy and Infectious Diseases – Sponsored Expert Panel" [https://www.niaid.nih.gov/sites/default/files/addendum-peanut-allergy-prevention-guidelines.pdf].
[18] *Id*.
[19] The Peanut Institute, "Peanut Facts." [http://www.peanut-institute.org/peanut-facts/]
[20] Boyce et al., Guidelines for the Diagnosis and Management of Food Allergy in the United States: Report of the NIAID-Sponsored Expert Panel. Journal of Allergy and Clinical Immunology 2010, Volume 126, Issue 6, S1 - S58.
[21] Sicherer SH, Munoz-Furlong A, Burks AW, Sampson HA. Prevalence of peanut and tree nut allergy in the US determined by a random digit dial telephone survey. J Allergy Clin Immunol 1999; 103:559-62.

studies have found reported peanut allergy prevalence to be as high as 2% in U.S. children.[22] Peanut allergy is likely caused by genetic and environmental factors.

Symptoms of peanut allergy include hives, red, itchy skin (atopic dermatitis or eczema), a runny or congested nose (rhinitis), sneezing or itchy, teary eyes; vomiting, stomach cramps or diarrhea, or swelling. In some cases, food allergic symptoms can involve the lungs and cardiovascular system and lead to a potentially life threatening reaction called anaphylaxis. Signs of this reaction may include flushed skin, hoarseness, throat tightness, wheezing, trouble breathing and low blood pressure or shock.[23] The agency concludes that the petitioner has satisfied the requirement in 21 CFR 101.14(a)(5) in that peanut allergy is a disease or health-related condition because there is damage to an organ, part, structure, or system of the body such that is does not function properly, or is a state of health leading to such dysfunctioning.

C. Safety Review

Under 21 CFR 101.14(b)(3)(ii), if the substance is to be consumed at other than decreased dietary levels, the substance must be a food or a food ingredient or a component of a food ingredient whose use at levels necessary to justify a claim has been demonstrated by the proponent of the claim, to FDA's satisfaction, to be safe and lawful under the applicable food safety provisions of the Act.

FDA evaluates whether the substance is "safe and lawful" under the applicable food safety provisions of the Act. For conventional foods, this evaluation involves considering whether the substance, which is either a food or an ingredient that is the source of the substance, is generally recognized as safe (GRAS), approved as a food additive, or authorized by a prior sanction issued by FDA (see 21 CFR 101.70(f)).

Ground peanuts are a specific food or a component of food, and thus, a substance as defined in 21 CFR 101.14(a)(2). Peanuts have a long history of human consumption as a food at a wide range of intake levels.[24] There are no regulatory additive or ingredient restrictions for peanut consumption for the population as a whole, or among different age groups, including consumption by infants, aged 4 through 10 months, and children up to 60 months who are identified as the target population in the proposed qualified health claim. The review of the evidence in this letter evaluates potential benefits of early introduction of peanut on the development of peanut allergy. However, regardless of the determination of benefit, pediatric guidelines for introduction of potentially allergenic foods, such as peanuts, to infants do not restrict or discourage feeding of such foods. Prior to the latest guidelines specific to peanut allergy,[25] the guidelines in the U.S. related to pediatric food allergy, issued by the NIH, National Institute of Allergy and Infectious Diseases (NIAID), recommended that solid foods, including potentially allergenic foods such as peanuts, should not be delayed beyond 4-6 months of age,

---

[22] Gupta RS, Springston EE, Warrier MR, Smith B, Kumar R, Pongracic J, et al. The prevalence, severity, and distribution of childhood food allergy in the United States. Pediatrics 2011;128:e9-17.
[23] American Academy of Allergy, Asthma, & Immunology, "Food Allergy Symptoms & Diagnosis" [http://www.aaaai.org/conditions-and-treatments/allergies/food-allergies].
[24] National Peanut Board, "History of Peanuts & Peanut Butter." [http://nationalpeanutboard.org/peanut-info/history-peanuts-peanut-butter.htm]
[25] See *supra*, note 17.

even for infants at risk of developing allergic disease (Boyce 2010). These NIH guidelines affirmed the policy statement by the American Academy of Pediatrics, published prior to the guidelines, stating that there was no evidence that delaying introduction of allergenic foods, such as peanut, beyond 4-6 months of age has a significant protective effect on the development of atopic disease (Greer, 2008). The U.S. recommendations on introduction of potentially allergenic foods to infants are similar to pediatric feeding recommendations found internationally, such as those found in Europe. The European Society for Pediatric Gastroenterology, Hepatology, and Nutrition recommendations on complementary feeding published, likewise, in 2008, concluded that avoidance or delayed introduction of potentially allergenic food had not been shown to reduce allergies (Agostoni, 2008). Thus, FDA concludes that under the preliminary requirements of 21 CFR 101.14(b)(3)(ii) that the petitioner has demonstrated to the agency's satisfaction that the use of ground peanuts for the population as a whole is safe and lawful under the applicable food safety provisions of the Act.

However, as discussed in Section I.B., peanut allergy is a type of food allergy. Peanuts are a major food allergen, as defined in section 201(qq)(1) of the Act (21 U.S.C. 321(qq)(1)), and foods containing them must be labeled in accordance with section 403(w) (21 U.S.C. 343(w)). As noted in section I.B., peanut allergy prevalence has been reported to be as high as 2% in children in the U.S.[26] and is the leading cause of death related to food-induced anaphylaxis in the U.S.[27] Peanuts should not be fed to infants and children who are allergic to peanuts.[28] Hypersensitivity reactions in peanut allergic infants and children represent a significant medical concern, as they may range from cutaneous reactions (e.g., urticaria, worsening eczema) to severe gastrointestinal reactions (food protein induced enterocolitis syndrome) or life-threatening anaphylaxis.

In addition, infants and children with severe eczema and/or egg allergy are at high risk of developing peanut allergy (Martin et al, 2015; Sampson, 2002). Moreover, symptoms associated with severe eczema[29] and/or egg allergy[30] may be similar to symptoms associated with peanut allergy[31] (e.g., hives, red, itchy skin, swelling). Consequently, certain symptoms an infant or child who has severe eczema or egg allergy may experience could also be the same symptoms experienced if the infant or child were allergic to peanuts. Therefore, parents and caregivers of infants with severe eczema and/or egg allergy should consult with their healthcare provider before feeding foods containing ground peanuts.[32]

Based on peanuts' extensive history of consumption as a food, including consumption in the age groups identified in the petition, FDA concludes that under the preliminary requirements of 21

---

[26] See *supra*, note 22.
[27] Bock SA, Munoz-Furlong A, Sampson HA. Fatalities due to anaphylactic reactions to foods. J Allergy Clin Immunol 2001;107:191-3. Bock SA, Munoz-Furlong A, Sampson HA. Further fatalities caused by anaphylactic reactions to food, 2001-2006. J Allergy Clin Immunol 2007;119:1016-8.
[28] See *supra*, note 17.
[29] https://medlineplus.gov/eczema.html
[30] http://www.mayoclinic.org/diseases-conditions/egg-allergy/basics/symptoms/con-20032721
[31] http://www.mayoclinic.org/diseases-conditions/peanut-allergy/basics/symptoms/con-20027898
[32] See *supra*, note 17.

CFR 101.14(b)(3)(ii), the petitioner has demonstrated to FDA's satisfaction that the use of ground peanuts are safe and lawful under the applicable food safety provisions of the Act. In Section IV, FDA sets forth factors under which it plans to exercise enforcement discretion for use of the qualified health claim.

II. The Agency's Consideration of a Qualified Health Claim

FDA has identified incident cases of peanut allergy as the endpoint to use in identifying a reduced risk of developing peanut allergy for purposes of a health claim. Although certain risk factors (i.e., egg allergy, severe eczema or both) for development of peanut allergy have been reported (Du Toit et al. 2015), FDA has not identified validated surrogate endpoints to use in assessing risk or risk reduction of peanut allergy development in individuals who have never been exposed to peanut. Thus, exposure to peanut is necessary to diagnose or confirm the presence or absence of peanut allergy development.

The development of peanut allergy may present clinically as peanut sensitization and/or peanut allergy, the latter of which represents clinically reactive peanut allergy. However, peanut sensitization (i.e., presence of IgE antibodies to peanut) may or may not be associated with food allergic disease or be an indicator of reactivity to peanut exposure (Boyce et al. 2010). Morbidity and mortality from peanut allergy is associated with adverse exposures to peanut in individuals with clinically reactive peanut allergy. Thus, FDA views clinically reactive peanut allergy as the endpoint for assessing the development of peanut allergy for the purposes of this health claim.

Peanut allergy is a type of IgE-mediated food allergy that can be diagnosed using various methods. The main methods include health history (i.e., well documented history of allergic reaction symptoms in temporal relation to peanut ingestion) in combination with positive diagnostic testing to peanut (by skin prick test (SPT) and/or in vitro methods demonstrating presence of peanut specific IgE antibodies), and/or positive oral food challenge to peanut in a supervised setting (Boyce et al. 2010; Sicherer and Sampson, 2014). Health history of adverse reactions to peanut alone is not definitive evidence of peanut allergy as this history may be biased by various factors unrelated to food ingestion. Also, although cut-offs (i.e., SPT size > 8 mm in diameter in infants (Peters et al. 2013) or peanut-specific IgE levels > 15 kUA/L (Sampson 2001), have been proposed as indicators of probable clinically reactive peanut allergy, skin prick tests and food specific IgE antibodies are generally regarded as markers of sensitization, and, without concomitant health history of adverse peanut exposure, are not definitive tests alone to document cases of clinically reactive food allergy (Boyce et al. 2010; Sicherer and Sampson, 2014). Rather, oral food challenge represents the method that corresponds most closely to the natural ingestion of food and provides the most definitive diagnosis of clinically reactive food allergy (Boyce et al. 2010).

The petition cited 243 articles/reports[33] as evidence to substantiate the relationship for the claim. The articles submitted consisted of 95 book chapters, review articles, or federal reports; 4 professional guidelines; 1 risk assessment; 16 comments or editorials; 15 abstracts written in English for articles written in a foreign language; 16 *in vitro* studies; 11 animal studies; 1

[33] See Docket No. FDA-2016-Q-0274.

newspaper article; 61 articles describing studies that did not measure peanut intake and/or peanut allergy in the study subjects, the substance and disease that are the subject of the proposed claim, (e.g., studies involving other types of interventions or studies of family history and allergies); 13 studies that were conducted on diseased populations (already diagnosed with peanut allergy prior to study enrollment); and 11 publications on studies relating to the consumption of peanuts and the emergence of peanut allergy.

In addition to the above publications, FDA identified 1 relevant intervention study (Perkin et al., 2016b) through a literature search for studies evaluating the relationship between peanut and risk of peanut allergy. FDA also considered the updated NIH NIAID Addendum Guidelines for the Prevention of Peanut Allergy in the United States.[34]

A. Assessment of Review Articles, Meta-analyses, and Book Chapters

Although useful for background information, the review articles, meta-analyses, and book chapters that were provided as part of your petition do not contain sufficient information on the individual studies reviewed and, therefore, FDA could not draw any scientific conclusions from this information. The lack of detailed information on studies summarized in the review articles, meta-analyses, and book chapters prevented FDA from determining whether the studies were flawed in critical elements such as design, conduct of studies, and data analysis. FDA must be able to review the critical elements of a study to determine whether any scientific conclusions can be drawn from it. As a result, the review articles, meta-analyses, and book chapters submitted with the petition or during the public comment period did not provide information from which scientific conclusions can be drawn regarding the substance-disease relationships claimed by the petitioner.

B. Assessment of Animal Studies

FDA uses animal studies as background information regarding mechanisms of action that might be involved in any relationship between the substance and the disease, and they can also be used to generate hypotheses or to explore a mechanism of action, but they cannot adequately support a relationship between the substance and the disease in humans. FDA did not consider the animal studies submitted with the petition as providing any supportive information about the substance-disease relationship because such studies cannot mimic the normal human physiology that may be involved in the risk reduction of peanut allergy, nor can the studies mimic the human body's response to the consumption of peanut. Therefore, FDA could not draw any scientific conclusions regarding the intake of peanut and the reduced risk of developing peanut allergy.

C. Assessment of the Intervention Studies

FDA evaluated three intervention studies described in 6 publications (Santos et al., 2015; Du Toit et al., 2013; Du Toit et al., 2015; Du Toit et al., 2016; Perkin et al., 2016a; Perkin et al., 2016b) that were designed to evaluate the relationship between the consumption of peanut and a reduced risk of peanut allergy for which the petition requested a qualified health claim. Scientific

[34] See *supra*, note 17.

conclusions concerning this relationship could not be drawn from 1 of the 3 intervention studies for the reasons discussed below.

The intervention study conducted by Santos et al. (2015) was designed to assess the utility of the basophil activation test to predict the severity and threshold of reactivity to peanut during oral food challenges. The oral food challenge is a diagnostic test designed to definitely diagnose food allergy and to elicit an immediate reaction to graded doses of the suspected allergenic food. Santos et al. administered oral food challenges to children 4-6 years of age who had peanut allergy (n=39), were peanut sensitized (n=39), or peanut tolerant (n=39). As this study provided peanut to children over a brief time interval (30 minutes to four hours) while contemporaneously testing for allergic reaction to peanut, it does not provide any information about the development of peanut allergy over time and following an extended period of peanut consumption. Nor does it provide information about the relationship between the consumption of peanut beginning in infancy and through early childhood and the risk of developing peanut allergy in childhood. Thus, scientific conclusions from this study could not be drawn about the relationship between the consumption of peanut and a reduced risk of developing a peanut allergy for which the petition requested a qualified health claim.

The LEAP (Learning Early About Peanut allergy) study was a randomized, open label, controlled intervention study of moderate methodological quality (DuToit et al., 2015). Infants were screened (DuToit et al., 2013)[35] and a total of 640 infants (at least 4 months but younger than 11 months of age) from the United Kingdom with severe eczema and/or egg allergy were enrolled. Infants were stratified into two cohorts on the basis of pre-existing sensitization to peanut, as determined by skin prick testing (SPT): one cohort had infants with no measureable wheal to a peanut skin test (SPT negative (*n*=542)) and the other had infants with measureable wheal responses (1-4 mm in diameter) (SPT positive (*n*=98)). The SPT-negative group was considered not sensitized to peanuts and the SPT-positive group was considered peanut sensitized with a wheal diameter of 1-4 mm. Each cohort was randomized to consume at least 6 grams of peanut protein per week over three or more meals (SPT-negative *n*=272; SPT-positive n=47) or avoid peanut consumption (SPT-negative *n*=280; SPT-positive n=51) until 60 months of age. All infants randomized to the peanut consumption group underwent a baseline oral food challenge before consuming peanut. Infants with a positive response to the oral food challenge (n=7) or reacted to peanut during the consumption period (n=8) did not consume or discontinued consuming peanut. Peanut protein was provided in the form of a snack food made from peanut butter and puffed maize or smooth peanut butter. The study had a 98.4% retention rate; 10 participants withdrew voluntarily or were lost to follow-up. Compliance with diets was assessed with validated food frequency questionnaires and peanut protein measured in bed dust samples. At evaluations conducted at 12 and 30 months of age, 75% of children in the peanut consumption group reported eating at least 6-7 g peanut protein per week over three meals. In general, infants adhered as defined by the study investigators to their assigned diets. The incidence of peanut allergy was determined by a positive oral food challenge at 60 months. Among the 542 infants in the SPT-negative group, 530 were randomized and analyzed for peanut allergy. At 60 months of age, 13.7% of the avoidance group and 1.9% of the consumption group were allergic to peanuts ($P < .001$). The absolute difference in risk between the groups was

[35] This study characterized the population screened for the LEAP intervention study. Baseline characteristics for infants screened for and enrolled in the LEAP intervention study are reported.

11.8% (95% confidence interval[36] 3.4 – 20.3; P<0.001) or an 86.1% relative reduction in the prevalence of peanut allergy. Among the 98 children in the SPT-positive group, all were randomized and analyzed for peanut allergy. At 60 months of age, 35.3% of the avoidance group and 10.6% of the consumption group were allergic to peanuts; the absolute difference between groups was 24.7% (95% CI, 4.9 to 43.3; P = 0.004) or a 70.0% relative reduction in the prevalence of peanut allergy. For both cohorts combined, 17.2% of the avoidance group and 3.2% of the consumption group were allergic to peanuts (P < .001). The absolute difference in risk between the groups was 14% or an 81% relative reduction in the prevalence of peanut allergy.

A follow-up to the LEAP study found that after twelve months of peanut avoidance, the prevalence of peanut allergy in the group that avoided peanuts during the study was statistically significantly higher than the group that consumed peanuts during the study (DuToit et al, 2016) (18.6% [52 of 280 participants] versus 4.8% [13 of 270 participants], P<0.001). Three new cases of allergy developed in each group. However, these cases did not result in a significant increase in the prevalence of peanut allergy in the group that consumed peanuts during the study (3.6% [10 of 274 participants] at 60 months and 4.8% [13 of 270 participants] at 72 months, P=0.25). Because this follow-up study did not provide peanut as an intervention, scientific conclusions from this study alone could not be drawn about the relationship between the consumption of peanut and a reduced risk of developing peanut allergy.

Perkin et al. (2016 b) was a moderate quality, randomized, controlled intervention trial, entitled "Enquiring About Tolerance" (EAT), that sought to determine whether the early introduction of common dietary allergens (peanut, cooked hen's egg, cow's milk, sesame, whitefish, and wheat) from 3 months of age in exclusively breast-fed infants in the general population (regardless of atopic status or family history of allergy) would prevent food allergies, as compared with infants who were exclusively breastfed for approximately 6 months. A total of 1303 infants from the United Kingdom were enrolled (Perkin 2016 a)[37]. Between 13 and 17 weeks of age, exclusively breastfed infants were randomly assigned to either a standard-introduction group (SIG, n= 651) or an early introduction group (EIG, N = 652). Infants in the standard-introduction group were instructed to consume no allergenic foods before 6 months of age and continued to be exclusively breastfed until about 6 months of age. Infants in the early introduction group were instructed to begin consuming 6 allergenic foods sequentially in generally randomized order (cow's milk, peanut, cooked egg, sesame, whitefish, and wheat) from 3 to 6 months of age in addition to being breastfed. In this general population of infants, about 24% of infants in both SIG and EIG groups had visible eczema. In the EIG, 9 children were sensitized to peanut (SPT range 1-4 mm) and 24 were sensitized to egg. The consumption target was 4 g of each allergenic food protein per week and in the case of peanut, equal to 2 teaspoons of peanut butter. The primary outcome was an oral food challenge-proven food allergy to one or more of the six early-introduction foods between 1 year and 3 years of age. Secondary outcomes were allergy to

[36] Confidence intervals are ranges that provide a statistical analysis of comparative measures of risk (e.g., relative risk, odds ratio and hazard ratio). Confidence intervals are significant when the entire range is less than or greater than "1" (e.g., 0.7-0.9 or 1.1-1.5). If the confidence interval includes "1" within its range, then it cannot be concluded that a relationship exists between the substance and the disease. See *supra*, note 6 [Section III. F].

[37] This study characterized the population screened for the EAT intervention study. The study design and baseline characteristics for infants screened for and enrolled in the EAT intervention study are reported.

individual foods and positive results on skin-prick testing for individual foods. Regarding consumption of peanuts, compliance with diets was assessed with validated food frequency questionnaires and peanut protein measured in bed dust samples. Overall compliance as defined by the investigators was 92% in the SIG and 42% in the EIG. In the EIG, by 6 months of age, 65% of infants consumed the recommended amount of peanut protein per week.

The incidence of peanut allergy was determined by positive oral food challenge at 12 or 36 months of age. The median age of first peanut consumption in the EIG was 20 weeks. In the SIG, 597 of 651 infants were analyzed for peanut allergy. In the EIG, 571 of 652 infants were analyzed for peanut allergy. Peanut allergy occurred in 1.2% of the participants in the EIG and in 2.5% of those in the SIG, representing a non-significant 51% lower relative risk in the early-introduction group (P = 0.11).

D. Assessment of Observational Studies

FDA evaluated 7 observational studies identified by the petition. Scientific conclusions about a relationship between peanut and a reduced risk of developing peanut allergy could not be drawn from these studies for the reasons discussed below.

One study (Du Toit et al., 2008) measured reported peanut allergy in children 4 through 18 years of age by questionnaire and confirmed the questionnaire identified peanut allergy (n=81) with clinical assessment (skin prick tests, peanut IgE, or both or an oral food challenge) in a subset of 47 children. As discussed above, skin prick tests or serum IgE blood levels alone are not sufficient to diagnose food allergy (Boyle et al., 2010; Sicherer and Sampson, 2014) and the number of children that were assessed by oral food challenge was not reported. This study also did not provide any information about peanut intake in the children that were clinically assessed for peanut allergy. While the study reported dietary intake data, the intake data was collected on a separate population of infants 4 to 24 months age and information about peanut allergy in these infants was not provided. Thus, scientific conclusions from this study could not be drawn about the relationship between the consumption of peanuts and a reduced risk of developing peanut allergy in the population for which the petition requested a qualified health claim.

Three studies did not report on the dietary assessment of peanut intake (Frank et al., 1999; Joseph et al., 2011; McGowan et al., 2015). We note that these studies also did not measure peanut allergy with an oral food challenge. As discussed above, oral food challenge represents the method that corresponds most closely to the natural ingestion of food and, provides the most definitive diagnosis of clinically reactive food allergy. Three other studies measured peanut intake in response to an oral food challenge (Johannsen et al., 2011; Ludman et al., 2013; Peters et al., 2015). The study duration was too short (approximately 30 minutes up to 4 hours) to provide any information about the long-term effect of peanut consumption on reducing the risk of peanut allergy.[38] Thus, scientific conclusions from these studies could not be drawn about the relationship between the consumption of peanut and a reduced risk of developing peanut allergy for which the petition requested a qualified health claim.

III. Strength of the Scientific Evidence

[38] See *supra*, note 6.

Below, the agency rates the strength of the total body of publicly available evidence. The agency conducts this rating evaluation by considering the study type (e.g., intervention, prospective cohort, case-control, cross-sectional), the methodological quality rating previously assigned, the number of studies and number of subjects per group, whether the body of scientific evidence supports a health claim relationship for the U.S. population or target subgroup, whether study results supporting the proposed claim have been replicated,[39] and the overall consistency[40] of the total body of evidence.[41] Based on the totality of the scientific evidence, FDA determines whether such evidence is credible to support a qualified health claim for the substance/disease relationship and, if so, considers what qualifying language should be included to convey the limits on the level of scientific evidence supporting the relationship and to prevent the claim from being misleading in other ways.

As discussed in section II, evidence relating to a relationship between peanut intake and a reduced risk of developing peanut allergy is limited to two intervention studies (DuToit et al., 2015; Perkin et al., 2016b) of moderate methodological quality. Both of these studies observed the development of peanut allergy in young children who began consuming peanuts in infancy compared to young children who avoided peanuts since infancy. In the LEAP study, infants between 4 and 10 months of age were randomized to either peanut consumption (SPT-negative n=272; SPT-positive n=47) of at least 6 grams of peanut protein per week over 3 meals or peanut avoidance (SPT-negative n=280; SPT-positive n=51) until 60 months of age. In the EAT study, infants between 3 and 6 months of age were randomized to either early peanut consumption (n = 595) of 4 grams of peanut protein over 2 feedings per week or peanut avoidance (n = 567) until 12 or 36 months of age. Peanut allergy was diagnosed by positive oral food challenge at 60 months and 12 or 36 months in the LEAP and EAT studies, respectively. Both studies were conducted in the United Kingdom and included a large number of subjects. Subjects in the LEAP study were required to have severe eczema, egg allergy, or both; whereas subjects in the EAT study were not restricted from enrollment based on atopic status.

Although both studies found a higher incidence of peanut allergy in young children who avoided peanuts since infancy, the result was not statistically significant in the EAT study. The LEAP study, on the other hand, found a statistically significant difference between the incidence of peanut allergy in children who consumed peanuts since infancy and those who did not ($P<0.001$). Thus, only one of the two intervention studies included in FDA's evaluation might be considered to show any credible evidence of a relationship between peanut consumption and reduced risk of developing peanut allergy.

Next, we consider the merits of the LEAP study in determining whether and to what extent the relationship between consumption of peanuts and the development of peanut allergy is scientifically supportable. As mentioned above, the LEAP study was a randomized, controlled, intervention study and enrolled a large number of subjects (n=650). In general, results from large, randomized, controlled intervention studies provide the strongest evidence for the claimed effect (Sempos et al., 1999). Moreover, the study was of moderate methodological quality and

[39] See *supra*, note 14.
[40] See *supra*, note 15.
[41] See *supra*, note 6 [Section III.F].

diagnosis of a clinical endpoint was determined by a definitively diagnostic method, i.e., positive oral food challenge. We also considered the statistical significance and magnitude of the risk reduction demonstrated in the LEAP study. There was a statistically significant 81% relative reduction in the development of peanut allergy by 60 months of age in the peanut consumption group compared to the peanut avoidance group. We note that, the greater the magnitude of the beneficial effect, the more likely the association may exist.[42] Here, we find a risk reduction of 81% to be a large difference in effect between the two groups.

Based on these factors, FDA concludes that the LEAP study provides credible evidence suggesting a possible relationship between consumption of peanuts and the development of peanut allergy in the specific population studied. However, consistency of findings among similar and different study designs is important for evaluating the strength of the scientific evidence and drawing conclusions about the substance-disease relationship. Without additional studies to corroborate the findings of the LEAP study and establish consistency and replicability of its results, FDA considers there to be limited evidence suggesting a possible relationship between peanut consumption during infancy and early childhood and the reduced risk of developing peanut allergy by 60 months of age.

Furthermore, in the absence of credible scientific evidence to suggest a possible substance-disease relationship outside the specific age range and atopic status of subjects enrolled in the LEAP study, the scope of the claim is limited to the age range and atopic status of subjects in the LEAP study (i.e., infants between 4 and 10 months of age with severe eczema and/or egg allergy). We note that 3 to 6 month-old infants without severe eczema and/or egg allergy were introduced to peanuts in the EAT study but a statistically significant relationship was not found when subjects were tested for peanut allergy at 12 or 36 months of age. This outcome suggests that the substance-disease relationship may not exist when peanut is introduced to infants in a younger age range without severe eczema and/or egg allergy and when consumption continues until less than 60 months of age. Therefore, FDA concludes that the qualified health claim is only supported for infants with severe eczema and/or egg allergy introduced to peanut between 4 and 10 months of age and who continue peanut consumption until 60 months of age.

In addition to the LEAP study, FDA also considered the National Academies report on *Finding a Path to Safety in Food Allergy*[43] and the Addendum Guidelines for the Prevention of Peanut Allergy in the United States.[44] We recognize that the purpose and scope of the NIH clinical feeding recommendations set for in the Addendum Guidelines for the Prevention of Peanut Allergy are separate and distinct from our review of scientific evidence to support a qualified health clam about a reduced risk of peanut allergy in food labeling.

---

[42] See supra, note 6 [section III.F].

[43] Finding a path to safety in food allergy: Assessment of the global burden, causes, prevention, management, and public policy. National Academies of Sciences, Engineering, and Medicine. 2017. Washington, DC: The National Academies Press.

[44] National Institute of Allergy and Infectious Diseases, "Addendum Guidelines for the Prevention of Peanut Allergy in the United States: Report of the National Institute of Allergy and Infectious Diseases – Sponsored Expert Panel" [https://www.niaid.nih.gov/sites/default/files/addendum-peanut-allergy-prevention-guidelines.pdf].

In sum, FDA has determined that the scientific evidence suggests a possible relationship between consumption of peanuts in infants with severe eczema and/or egg allergy, beginning between 4 and 10 months of age and continuing until 60 months of age, and a reduced risk of developing peanut allergy by 60 months of age. The evidence supporting this possible relationship is limited to the LEAP study.

IV. Other Enforcement Discretion Factors

A qualified health claim about foods containing ground peanuts and a reduction in risk of developing peanut allergy on the label or in the labeling of conventional foods is required to meet all applicable statutory and regulatory requirements under the Federal Food, Drug, and Cosmetic Act, with the exception of the requirement that a health claim meet the significant scientific agreement standard and the requirement that the claim be made in accordance with an authorizing regulation. Other enforcement discretion factors specific to qualified health claims for foods containing ground peanuts are discussed below.

A. Description of Target Population

The LEAP study suggests a relationship between introduction of foods containing ground peanuts and a reduced risk of developing peanut allergy (1) in infants with severe eczema and/or egg allergy, (2) when ground peanuts are introduced between 4 months and 10 months of age, and (3) when ground peanuts continue to be consumed until 60 months of age (or 5 years of age). Without this information, the agency would consider the qualified health claim to be misleading under sections 403(a)(1) and 201(n) of the Act (343 U.S.C. 343(a)(1) and 321(n)).

Section 403(a)(1) states that food is misbranded if its labeling is false or misleading in any particular. Section 201(n) states that, in determining whether labeling is misleading, the agency shall take into account not only representations made about the product, but also the extent to which the labeling fails to reveal facts material in light of such representations made or suggested in the labeling or material with respect to the consequences which may result from use of the article to which the labeling relates under the conditions of use as are customary or usual. Thus, the omission of certain material facts from the label or labeling on a food causes the product to be misbranded within the meaning of sections 403(a)(1) and 201(n).

The qualified health claim requested by the petitioner will appear on the label of foods containing ground peanuts. The qualified health claim makes the representation that consuming peanuts may reduce the risk of developing peanut allergy. However, the LEAP study, the only credible scientific evidence supporting this relationship, was specifically conducted in infants with severe eczema and/or egg allergy between the ages of 4 and 10 months who continued consumption of peanuts until 60 months of age. Without this information, the claim would imply that the relationship is supported for all ages, regardless of atopic status, and regardless of the duration of consumption. The agency therefore concludes that this information is material in light of the representation that consumption of peanut may reduce the risk of developing peanut allergy. Thus, omission of this information from the claim language would cause the labeling of the food containing ground peanuts to be misleading under sections 403(a)(1) and 201(n) of the Act.

Therefore, the agency is considering, as a factor in the exercise of its enforcement discretion that the claim language include the information enumerated in (1)-(3) above.

B. Level of Consumption

The general requirements for health claims provide that, if the claim is about the effects of consuming the substance at other than decreased dietary levels, the level of the substance must be sufficiently high and in an appropriate form to justify the claim. Where no definition for "high" has been established, the claim must specify the daily dietary intake necessary to achieve the claimed effect (21 CFR 101.14(d)(2)(vii)). However, the agency finds that this provision should not be applied to these qualified health claims for ground peanuts. The LEAP study was not designed to evaluate a dose-response relationship and did not provide dose response data. Specifying a recommended daily intake level of ground peanuts to be included in the claim language based on the level of intake from one study that did not evaluate a dose response would imply consistency in the body of evidence and more certainty about the level of effect than exists for the population that is the subject of the qualified health claim.[45] Therefore, FDA does not have a sufficient basis to identify a daily dietary intake level necessary to achieve the claimed effect, or to set forth, as a factor in the exercise of its enforcement discretion, an amount of ground peanuts that would be necessary for a food bearing the qualified health claim to contain in order to be eligible to bear the claim. Furthermore, as discussed in Section IV.D., the claim will direct consumers to their healthcare provider before feeding ground peanuts. Healthcare providers can provide individual guidance on the introduction of ground peanuts to an infant's diet, including amount and timing of feeding ground peanuts.[46]

Therefore, the FDA is not specifying any minimum level of intake of ground peanuts to be considered as a factor in the exercise of its enforcement discretion for a qualified health claim about a reduced risk of developing peanut allergy. Furthermore, the agency would consider any label or labeling suggesting a specific level of ground peanuts to be useful in achieving a reduced risk of developing peanut allergy for the general healthy population to be false and misleading under Section 403 (a) of the Act. Further, FDA would monitor and evaluate for possible enforcement action situations where foods that bear the qualified health claim for introduction of foods containing ground peanuts between 4 and 10 months of age and reduced risk of developing peanut allergy that contain ground peanuts in trivial amounts.

C. Disqualifying Nutrient Levels

Under the general requirements for health claims, a health claim may not be made on the label or in labeling when the label represents or purports that a food is for infants and toddlers less than 2 years of age except if the claim is specifically provided for by regulation (21 CFR 101.14(e)(5)) . FDA intends to consider exercising enforcement discretion for the use of the qualified health claim, not specifically required by regulation, on the label or in labeling for such foods. With respect to disqualifying nutrient levels, a food may not bear a health claim if that food exceeds any of the disqualifying nutrient levels for total fat, saturated fat, cholesterol, or sodium

[45] See *supra*, note 6 [Section III.H.]

[46] We note that the NIAID Addendum Guidelines provide clinical recommendations for feeding peanut protein to infants and young children for health care professionals to consider when implementing the guidelines.

established in § 101.14(a)(4), as required by 21 CFR 101.14(e)(3). Section 101.14 applies to all health claims regardless of types of diseases and health-related conditions. Disqualifying total fat levels are above 13.0 g per Reference Amount Customarily Consumed (RACC), per label serving size and per 50 g if the RACC is 30 g or less or 2 tablespoons or less for individual foods. Disqualifying saturated fat levels are above 4.0 g per RACC, per label serving size and per 50 g if the RACC is 30 g or less or 2 tablespoons or less for individual foods. Disqualifying cholesterol levels are above 60 mg per RACC, per label serving size and per 50 g if the RACC is 30 g or less or 2 tablespoons or less for individual foods. Disqualifying sodium levels are 480 mg per RACC, per label serving size and per 50 g if the RACC is 30 g or less or 2 tablespoons or less for individual foods.

The general requirements for health claims also provide for FDA to authorize a health claim for a food despite the fact that a nutrient in the food exceeds the disqualifying level, if the agency finds that such a claim will assist consumers in maintaining healthy dietary practices (21 CFR 101.14(e)(3)). In such cases, the label must also bear a disclosure statement that complies with 21 CFR 101.13(h), highlighting the nutrient that exceeds the disqualifying level, unless subject to an exception from the need for a disclosure statement (21 CFR 101.14(e)(3)). One such exception is food intended specifically for use by infants and children less than 2 years of age. Therefore, if the qualified health claim appears on a food that exceeds a disqualifying nutrient level, and the food is represented or purported for infants and children less than 2 years of age, a disclosure statement would not be required by section 101.13(h).

Ground peanuts and certain foods that would contain ground peanuts, such as smooth peanut butter, exceed the total fat disqualifying level per RACC and per 50g. Certain foods that contain ground peanuts, such as smooth peanut butter, also exceed the total fat and saturated fat disqualifying levels per 50g, due to the fact that they have small RACCs. FDA considers that an appropriately qualified health claim about consumption of ground peanuts could assist consumers in maintaining healthy dietary practices, based on the suggestive evidence of a relationship between early consumption of ground peanuts in infants with severe eczema and/or egg allergy and the reduced risk of developing peanut allergy. Thus, FDA intends to exercise enforcement discretion for foods that bear the qualified health claim and exceed the disqualifying levels for total fat and saturated fat set forth in 21 CFR 101.14(a)(4). FDA believes that it is appropriate to consider, as a factor in the exercise of its enforcement discretion, that when the total fat or saturated fat level in the food exceeds the disqualifying level as defined by 21 CFR 101.14(a)(4), the label bear a disclosure statement (e.g., See nutrition information for total fat content) that complies with 21 CFR 101.13(h).[47] The exercise of our enforcement discretion

[47] We note that 21 CFR 101.13(h) contains exceptions to the need for a disclosure statement that includes an exception for food intended specifically for use by infants and children less than 2 years. We also note that the final rule entitled "Food Labeling: Revision of the Nutrition and Supplement Facts Labels" (81 Fed. Reg. 33742; May 27, 2016) changed the declaration required for certain nutrients, including total fat and saturated fat, on foods, other than infant formula, represented or purported to be specifically for infants and young children, and changed the age category for which the nutrient declarations are required from infants and children less than 2 years of age to infants through 12 months of age and children 1 through 3 years of age. Thus, section 101.9(j)(5)(i) now requires, among other nutrients, the declaration of total fat and saturated fat to be declared on foods, other than infant formula, represented or purported to be specifically for infants through 12 months of age and children 1 through 3 years of age on nutrition labeling. We plan to address, as appropriate and as time and resources permit, the impact of the changes in nutrient declarations in the final rule to other regulations, such as 21 CFR 101.13(h) and 101.14 related to nutrient disclosure requirements, in separate rulemaking actions (see 81 Fed. Reg. 33742 at 33751).

would not be necessary for food bearing the qualified health claim intended specifically for use by infants and children less than 2 years for which a disclosure statement, as described in section 101.13(h), is not required. FDA will also consider, as a factor in the exercise of its enforcement discretion, that foods that contain ground peanuts that bear a qualified health claim for early consumption of ground peanuts in infants with severe eczema and/or egg allergy and the reduced risk of developing peanut allergy, meet the requirements for the sodium and cholesterol disqualifying levels, as required by sections 101.14(a)(4) and (e)(3), and disclosure statements, as required by section 101.13(h).

D. Additional Claim Language

1. Consulting with a healthcare provider before introduction of foods containing ground peanuts to infants and children with severe eczema and/or egg allergy

Having evaluated the LEAP study and evidence related to the prevalence of peanut allergy among infants and children, FDA concludes that additional language is needed to ensure safe feeding of foods containing ground peanuts to infants with severe eczema and/or egg allergy.

First, the LEAP study excluded infants who demonstrated strong peanut sensitization to the skin prick test (i.e., infants with SPT-induced wheal diameters greater than 4mm). These infants totaled 9.1% of infants (76 of 834 infants) with severe eczema and/or egg allergy screened for enrollment. Because these infants were not included in the study, the safety and effectiveness of peanut consumption in this population remain unknown (see DuToit et al., 2015). However, the claim language does not inform caregivers of infants with severe eczema and/or egg allergy that the relationship between peanut consumption and reduced risk of developing peanut allergy is not supported for infants with strong peanut sensitization. More importantly, even if caregivers were aware of this, they are unlikely to know whether their infant has strong peanut sensitization. Such a determination can only be made by consulting with a healthcare provider. Therefore, FDA concludes that caregivers should be advised to consult a healthcare provider before deciding whether to feed foods containing ground peanuts to their infant with severe eczema and/or egg allergy. Further, FDA concludes it is necessary to qualify the target population of the claim language to be "most infants with severe eczema and/or egg allergy." The target population does not include infants with severe eczema and/or egg allergy with strong peanut sensitization because such infants were not included in the LEAP study.

Second, among infants who met criteria for enrollment in the LEAP study, several were determined to have peanut allergy before peanut consumption began. Seven infants failed the baseline OFC and therefore had challenge-proven peanut allergy. Thus, even among the population of infants supported by the claim language, there may be infants for whom peanut consumption is not appropriate and presents a safety risk. Indeed, infants with eczema are known to be 11 times more likely to have peanut allergy by the age of 12 months than infants without eczema (Martin et al., 2015) and peanut allergy has been observed to be more prevalent among infants and children with egg allergy (Sampson, 2012.). Unless their infant has had a previous reaction to peanut exposure, which is unlikely at such a young age, caregivers will not

know whether their infant with severe eczema and/or egg allergy has peanut allergy. As such, testing and evaluation by a healthcare provider are necessary to diagnose pre-existing peanut allergy. In light of this and the potential for serious adverse health reactions to result from consumption of peanuts, including death related to food-induced anaphylaxis, FDA concludes that caregivers of infants with severe eczema and/or egg allergy should be advised to consult a healthcare provider before feeding foods containing ground peanuts.

The claim language proposed by Assured Bites, Inc. is not sufficient to prevent consumers from being misled in part because it does not make clear that a healthcare professional should be consulted before introducing ground peanuts into the diet of an infant with severe eczema and/or egg allergy, or that not all infants with severe eczema and/or egg allergy should be fed ground peanuts. The articulation of the relationship between the consumption of peanut and a reduced risk of developing peanut allergy could mislead consumers into thinking that ground peanuts are appropriate to feed to infants with severe eczema and/or egg allergy and who may be peanut allergic or have symptoms of peanut allergy. The agency considers it appropriate to include, as a factor in the exercise of its enforcement discretion, that the qualified claim state "most" infants with severe eczema or egg allergy and additional language be added to the claim stating:

> **If your infant has severe eczema and/or egg allergy, check with your infant's healthcare provider before feeding foods containing ground peanuts.**

Without this information, and without the bold text, the agency would consider the qualified health claim to be misleading under sections 403(a)(1) and 201(n) of the FD&C Act because it would fail to reveal facts material with respect to consequences which may result from the food, if consumed by infants and children that are the subject of the claim. FDA has concluded that this language, in bold type, is necessary in light of the significant public health risk that could be created by the feeding of foods containing ground peanuts to some infants with severe eczema and/or egg allergy.[48]

V. Conclusions

Based on FDA's consideration of the scientific evidence submitted with the petition and other pertinent scientific evidence, FDA concludes that that the current scientific evidence is appropriate for consideration of a qualified health claim regarding the relationship between the consumption of foods containing ground peanuts and a reduced risk of developing peanut allergy, provided that the qualified health claims are worded so as not to mislead consumers.

The agency has concluded that certain language in the proposed claims is not appropriate for inclusion in the qualified health claim. The language "emerging clinical research" to describe the evidence supporting the relationship between consumption of peanuts and reduced risk of developing peanut allergy mischaracterizes the strength of the evidence and is misleading because it suggests that there is currently more scientific evidence available than a single

[48] See *memo to file*, Docket No. FDA-2016-Q-0274, Rationale for requiring additional safety language to accompany the qualified health claim.

intervention study (DuToit et al., 2015) or that more evidence will soon be available to support such a relationship. The language "initial clinical study" is also misleading as it suggests that more evidence will soon be available to support such a relationship. Furthermore, the proposed claims describe "early introduction of peanuts to infants aged 4 to 60 months" or "early introduction of peanuts to infants." However, these are not accurate descriptions of the population, the age of introduction, and the duration of continued consumption of foods containing ground peanuts supported by the evidence. In this intervention study, the reduced risk of peanut allergy was observed in infants with severe eczema and/or egg allergy who began consuming peanut protein between 4 and 10 months of age and continued consumption up to 60 months of age. Without this information, the evidence does not support the proposed claim.

The language of one of the proposed claims states that the introduction of peanuts is for "infants ready for solid foods." FDA agrees that other solid foods should be introduced before ground peanuts to show that the infant is developmentally ready. [49] FDA has revised the language from the proposed qualified health claim to state that the introduction of foods containing ground peanuts is for infants "who are already eating solid foods."

In light of the above considerations, FDA intends to consider the exercise of its enforcement discretion for the following qualified health claim:

> For most infants with severe eczema and/or egg allergy who are already eating solid foods, introducing foods containing ground peanuts between 4 and 10 months of age and continuing consumption may reduce the risk of developing peanut allergy by 5 years of age. FDA has determined, however, that the evidence supporting this claim is limited to one study.
>
> **If your infant has severe eczema and/or egg allergy, check with your infant's healthcare provider before feeding foods containing ground peanuts.**

FDA intends to consider exercising its enforcement discretion for the above qualified health claim when all the factors for enforcement discretion identified in this letter are met.

Please note that scientific information is subject to change, as are consumer consumption patterns. FDA intends to evaluate new information that becomes available to determine whether it necessitates a change in this decision. For example, scientific evidence may become available that will support significant scientific agreement that will no longer support the use of the above qualified health claim or that may raise safety concerns about the substance that is the subject of the claim.

Sincerely,

Douglas Balentine, Ph.D.

[49] See *supra*, note 17.

Director
Office of Nutrition
and Food Labeling
Center for Food Safety
and Applied Nutrition

References

Boyce J.A., Assa'ad A, et al. (2010). Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. J Allergy Clin Immunol. 126(6 Suppl),S1–S58

Du Toit, G., Sayre, P. H., Roberts, G., Sever, M. L., Lawson, K., Bahnson, H. T., Lack, G. (2016). Effect of Avoidance on Peanut Allergy after Early Peanut Consumption. N Engl J Med.

Du Toit, G. R., G. Sayre, P. H. Bahnson, H. T. Radulovic, S. Santos, A. F. Brough, H. A. Phippard, D. Basting, M. Feeney, M. Turcanu, V. Sever, M. L. Gomez Lorenzo, M. Plaut, M. Lack, G. (2015). Randomized trial of peanut consumption in infants at risk for peanut allergy. N Engl J Med, 372(9), 803-813.

Du Toit, G., Roberts, G., Sayre, P. H., Plaut, M., Bahnson, H. T., Mitchell, H., Lack, G. (2013). Identifying infants at high risk of peanut allergy: the Learning Early About Peanut Allergy (LEAP) screening study. J Allergy Clin Immunol, 131(1), 135-143 e131-112.

Federal Judicial Center. 2000. Reference Manual on Scientific Evidence, 2nd Edition, p. 93

Frank, L., Marian, A., Visser, M., Weinberg, E., & Potter, P. C. (1999). Exposure to peanuts in utero and in infancy and the development of sensitization to peanut allergens in young children. Pediatr Allergy Immunol, 10(1), 27-32.

Institute of Medicine, National Academy of Sciences (IOM). (2005). Dietary Supplements: A Framework for Evaluating Safety. Chapter 7, Categories of Scientific Evidence – In Vitro Data. The National Academies Press, Washington, D.C.

Ludman, S., Ballabeni, P., Eigenmann, P. A., & Wassenberg, J. (2013). Predicting positive food challenges in children sensitised to peanuts/tree nuts. Pediatr Allergy Immunol, 24(3), 276-281.

Johannsen, H., Nolan, R., Pascoe, E. M., Cuthbert, P., Noble, V., Corderoy, T., Prescott, S. L. (2011). Skin prick testing and peanut-specific IgE can predict peanut challenge outcomes in preschool children with peanut sensitization. Clin Exp Allergy, 41(7), 994-1000.

Joseph, C. L., Ownby, D. R., Havstad, S. L., Woodcroft, K. J., Wegienka, G., MacKechnie, H., Johnson, C. C. (2011). Early complementary feeding and risk of food sensitization in a birth cohort. J Allergy Clin Immunol, 127(5), 1203-1210 e1205.

McGowan, E. C., Bloomberg, G. R., Gergen, P. J., Visness, C. M., Jaffee, K. F., Sandel, M., Wood, R. A. (2015). Influence of early-life exposures on food sensitization and food allergy in an inner-city birth cohort. J Allergy Clin Immunol, 135(1), 171-178.

Perkin, M. R., Logan, K., Marrs, T., Radulovic, S., Craven, J., Flohr, C., & Lack, G. (2016a). Enquiring About Tolerance (EAT) study: Feasibility of an early allergenic food introduction regimen. J Allergy Clin Immunol, 137(5), 1477-1486 e1478.

Perkin, M. R., Logan, K., Tseng, A., Raji, B., Ayis, S., Peacock, J., Lack, G. (2016b). Randomized Trial of Introduction of Allergenic Foods in Breast-Fed Infants. N Engl J Med, 374(18), 1733-1743.

Peters R.L., Allen KJ, Dharmage SC, Tang ML, Koplin JJ, Ponsonby AL, et al. (2013). Skin prick test responses and allergen-specific IgE levels as predictors of peanut, egg, and sesame allergy in infants. J Allergy Clin Immunol 132, 874-80.

Peters, R. L., Allen, K. J., Dharmage, S. C., Lodge, C. J., Koplin, J. J., Ponsonby, A. L., Gurrin, L. C. (2015). Differential factors associated with challenge-proven food allergy phenotypes in a population cohort of infants: a latent class analysis. Clin Exp Allergy, 45(5), 953-963.

Sampson HA. Clinical practice. Peanut allergy. (2002). N Engl J Med 346, 1294-9.

Santos, A. F. D. T., G. Douiri, A. Radulovic, S. Stephens, A. Turcanu, V. Lack, G. (2015). Distinct parameters of the basophil activation test reflect the severity and threshold of allergic reactions to peanut. J Allergy Clin Immunol, 135(1), 179-186.

Spilker, B. 1991. Guide to Clinical Studies. Raven Press, New York, New York, pp. 59-64.

Wilson, E.B. 1990. An Introduction to Scientific Research. Dover Publications, New York, pp. 46-48.

Appendix 1

Book chapters, review articles, or federal reports:

Allen, K. J., Koplin., J. J. (2016). Prospects for Prevention of Food Allergy. J Allergy Clin Immunol Pract.

Anagnostou, K. (2015). Recent advances in immunotherapy and vaccine development for peanut allergy. Ther Adv Vaccines, 3(3), 55-65.

Anagnostou, K., Clark., A. (2014). Peanut immunotherapy. Clin Transl Allergy, 4, 30.

Anagnostou, K., Clark., A. (2015). The management of peanut allergy. Arch Dis Child, 100(1), 68-72.

Anagnostou, K., Clark., A. (2016). Oral Immunotherapy for Peanut Allergy. Annu Rev Med, 67, 375-385.

Anderson, J. A. (1997). Milk, eggs and peanuts: food allergies in children. Am Fam Physician, 56(5), 1365-1374.

Antolin-Amerigo, D., Manso, L., Caminati, M., de la Hoz Caballer, B., Cerecedo, I., Muriel, A., Rodriguez-Rodriguez, M., Barbarroja-Escudero, J., Sanchez-Gonzalez, M. J., Huertas-Barbudo, B., Alvarez-Mon, M. (2016). Quality of life in patients with food allergy. Clin Mol Allergy, 14, 4.

Bahna, S. L., Mayer, C. W. (2005). Food allergy: manifestations, diagnosis and management. Expert Rev Clin Immunol, 1(1), 133-143.

Beausoleil, J. L., Fiedler., J., Spergel, J. M. (2007). Food Intolerance and childhood asthma: what is the link? Paediatr Drugs, 9(3), 157-163.

Bergmann, M. M., Caubet, J. C., Boguniewicz, M., Eigenmann, P. A. (2013). Evaluation of food allergy in patients with atopic dermatitis. J Allergy Clin Immunol Pract, 1(1), 22-28.

Beyer, K. (2007). Hypoallergenicity: a principle for the treatment of food allergy. Nestle Nutr Workshop Ser Pediatr Program, 59, 37-43; discussion 43-37.

Brenna, J. T. (2011). Animal studies of the functional consequences of suboptimal polyunsaturated fatty acid status during pregnancy, lactation and early post-natal life. Matern Child Nutr, 7 Suppl 2, 59-79.

Brough, H. A., Turner, P. J., Wright, T., Fox, A. T., Taylor, S. L., Warner, J. O., Lack, G. (2015). Dietary management of peanut and tree nut allergy: what exactly should patients avoid? Clin Exp Allergy, 45(5), 859-871.

Burbank, A. J., Sood, P., Vickery, B. P., Wood, R. A. (2016). Oral Immunotherapy for Food Allergy. Immunol Allergy Clin North Am, 36(1), 55-69.

Burks, A. W. (2008). Peanut allergy. Lancet, 371(9623), 1538-1546.

Burks, W., Lehrer, S. B. Bannon, G. A. (2004). New approaches for treatment of peanut allergy: chances for a cure. Clin Rev Allergy Immunol, 27(3), 191-196.

Chan, S. M., Dumitru, C., Turcanu, V. (2012). Molecular diagnosis of peanut allergy. Expert Rev Mol Diagn, 12(8), 879-891.

Chandra, R. K. (1997). Food hypersensitivity and allergic disease: a selective review. Am J Clin Nutr, 66(2), 526S-529S.

Chehade, M. (2007). IgE and non-IgE-mediated food allergy: treatment in 2007. Curr Opin Allergy Clin Immunol, 7(3), 264-268.

Cianferoni, A., Muraro, A. (2012). Food-induced anaphylaxis. Immunol Allergy Clin North Am, 32(1), 165-195.

de Leon, M. P., Rolland, J. M. O'Hehir, R. E. (2007). The peanut allergy epidemic: allergen molecular characterisation and prospects for specific therapy. Expert Rev Mol Med, 9(1), 1-18.

Deol, S., Bird, J. A. (2014). Current opinion and review on peanut oral immunotherapy. Hum Vaccin Immunother, 10(10), 3017-3021.

Du Toit, G. S., A. Roberts, G. Fox, A. T. Smith, P. Lack, G. (2009). The diagnosis of IgE-mediated food allergy in childhood. Pediatr Allergy Immunol, 20(4), 309-319.

Edlich, R. F. Cochran, A., Greene, J. A. Woode, D. R. Gubler, K. D. Long, W. B., 3rd. (2011). Advances in the treatment of peanut allergy: a case report. J Emerg Med, 40(6), 633-636.

Elizur, A., Katz, Y. (2016). Timing of allergen exposure and the development of food allergy: treating before the horse is out of the barn. Curr Opin Allergy Clin Immunol.

Fleischer, D. M. (2007). The natural history of peanut and tree nut allergy. Curr Allergy Asthma Rep, 7(3), 175-181.

Fleischer, D. M., Spergel, J. M. Assa'ad, A. H. Pongracic, J. A. (2013). Primary prevention of allergic disease through nutritional interventions. J Allergy Clin Immunol Pract, 1(1), 29-36.

Fogg, M. I. Spergel, J. M. (2003). Management of food allergies. Expert Opin Pharmacother, 4(7), 1025-1037.

Greenhawt, M. (2010). The role of food allergy in atopic dermatitis. Allergy Asthma Proc, 31(5), 392-397.

Greenhawt, M. (2015). The Learning Early About Peanut Allergy Study: The Benefits of Early Peanut Introduction, and a New Horizon in Fighting the Food Allergy Epidemic. Pediatr Clin North Am, 62(6), 1509-1521.

Harsono, A. Partana., J. S. Partana, L. (1990). The allergy management of bronchial asthma in children in Surabaya. Paediatr Indones, 30(9-10), 266-269.

Hill, J. H. Whitham, S. A. (2014). Control of virus diseases in soybeans. Adv Virus Res, 90, 355-390.

Hourihane, J. O. (2002). Recent advances in peanut allergy. Curr Opin Allergy Clin Immunol, 2(3), 227-231.

Hourihane, J. O. (2011). Peanut allergy. Pediatr Clin North Am, 58(2), 445-458, xi.

Husby, S. (2008). Food allergy as seen by a paediatric gastroenterologist. J Pediatr Gastroenterol Nutr, 47 Suppl 2, S49-52.

Ismail, I. H., Tang, M. L. (2012). Oral immunotherapy for the treatment of food allergy. Isr Med Assoc J, 14(1), 63-69.

Jarvinen, K. M. (2011). Food-induced anaphylaxis. Curr Opin Allergy Clin Immunol, 11(3), 255-261.

Jarvinen, K. M., Fleischer, D. M. (2012). Can we prevent food allergy by manipulating the timing of food exposure? Immunol Allergy Clin North Am, 32(1), 51-65.

Kostadinova, A. I., Willemsen, L. E. Knippels, L. M. Garssen, J. (2013). Immunotherapy - risk/benefit in food allergy. Pediatr Allergy Immunol, 24(7), 633-644.

Kramer, M. S., Kakuma, R. (2012). Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child. Cochrane Database Syst Rev, 9, CD000133.

Kramer, M. S., Kakuma, R. (2014). Maternal dietary antigen avoidance during pregnancy or lactation, or both, for preventing or treating atopic disease in the child. Evid Based Child Health, 9(2), 447-483.

Krull, C. E. (1998). Inhibitory interactions in the patterning of trunk neural crest migration. Ann N Y Acad Sci, 857, 13-22.

Kurowski, K., Boxer, R. W. (2008). Food allergies: detection and management. Am Fam Physician, 77(12), 1678-1686.

Lee, C. W., Sheffer, A. L. (2003). Peanut allergy. Allergy Asthma Proc, 24(4), 259-264.
Li, X. M. (2005). Beyond allergen avoidance: update on developing therapies for peanut allergy. Curr Opin Allergy Clin Immunol, 5(3), 287-292.

Liu, M., Burks, A. W. Green, T. D. (2015). Tree nut allergy: risk factors for development, mitigation of reaction risk and current efforts in desensitization. Expert Rev Clin Immunol, 11(5), 673-679.

Lomas, J. M., Jarvinen, K. M. (2015). Managing nut-induced anaphylaxis: challenges and solutions. J Asthma Allergy, 8, 115-123.

Lomidze, N. G., T. Gotua, M. Gotua (2015). IgE-mediated food allergy - current problems and future perspectives (review). Georgian Med News(238), 73-78.

Longo, G., Berti, I., Burks, A. W. Krauss, B. Barbi, E. (2013). IgE-mediated food allergy in children. Lancet, 382(9905), 1656-1664.

MacDermott, R. P. (2007). Treatment of irritable bowel syndrome in outpatients with inflammatory bowel disease using a food and beverage intolerance, food and beverage avoidance diet. Inflamm Bowel Dis, 13(1), 91-96.

MacDonald, T. T., Di Sabatino, A. (2009). The immunologic basis for gastrointestinal food allergy. Curr Opin Gastroenterol, 25(6), 521-526.

McLean, S.. Sheikh, A. (2010). Does avoidance of peanuts in early life reduce the risk of peanut allergy? BMJ, 340, c424.

Mehta, H., Groetch, M. Wang, J. (2013). Growth and nutritional concerns in children with food allergy. Curr Opin Allergy Clin Immunol, 13(3), 275-279.

Miller, D. S., Brown, M. P., Howley, P. M., Hayball, J. D. (2012). Current and emerging immunotherapeutic approaches to treat and prevent peanut allergy. Expert Rev Vaccines, 11(12), 1471-1481.

Misak, Z. (2011). Infant nutrition and allergy. Proc Nutr Soc, 70(4), 465-471.
Moneret-Vautrin, D. A. M., M. (2005). Adult food allergy. Curr Allergy Asthma Rep, 5(1), 80-85.

Narisety, S. D., Keet, C. A. (2012). Sublingual vs oral immunotherapy for food allergy: identifying the right approach. Drugs, 72(15), 1977-1989.

Novak, R. W., Martin, C. R., Orsini, E. N. (1983). Hemolytic-uremic syndrome and T-cryptantigen exposure by neuraminidase-producing pneumococci: an emerging problem? Pediatr Pathol, 1(4), 409-413.

Nowak-Wegrzyn, A., Sampson, H. A. (2011). Future therapies for food allergies. J Allergy Clin Immunol, 127(3), 558-573; quiz 574-555.

Nurmatov, U., Venderbosch, I. Devereux, G. Simons, F. E. Sheikh, A. (2012). Allergen-specific oral immunotherapy for peanut allergy. Cochrane Database Syst Rev, 9, CD009014.

O'Hehir, R. E., Sandrini, A. Anderson, G. P. Rolland, J. M. (2007). Sublingual allergen immunotherapy: immunological mechanisms and prospects for refined vaccine preparation. Curr Med Chem, 14(21), 2235-2244.

O'Keefe, A. W., De SSchryver, S. Mill, J. Mill, C. Dery, A. Ben-Shoshan, M. (2014). Diagnosis and management of food allergies: new and emerging options: a systematic review. J Asthma Allergy, 7, 141-164.

Pansare, M. Kamat, D. (2010). Peanut allergy. Curr Opin Pediatr, 22(5), 642-646.

Patel, B. Y., Volcheck, G. W. (2015). Food Allergy: Common Causes, Diagnosis, and Treatment. Mayo Clin Proc, 90(10), 1411-1419.

Perr, H. A. (2004). Novel foods to treat food allergy and gastrointestinal infection. Curr Gastroenterol Rep, 6(3), 254-260.

Pham, T. S. Rudner, E. J. (2000). Peanut allergy. Cutis, 65(5), 285-289.

Pons, L. P., K. Burks, W. (2005). Towards immunotherapy for peanut allergy. Curr Opin Allergy Clin Immunol, 5(6), 558-562.

Pratico, A. D., Leonardi, S. (2015). Immunotherapy for food allergies: a myth or a reality? Immunotherapy, 7(2), 147-161.

Riascos, J. J. W., A. K. Weissinger, S. M. Burks, A. W. (2010). Hypoallergenic legume crops and food allergy: factors affecting feasibility and risk. J Agric Food Chem, 58(1), 20-27.

Rolland, J. M., Gardner, L. M., O'Hehir, R. E. (2009). Allergen-related approaches to immunotherapy. Pharmacol Ther, 121(3), 273-284.

Sampson, H. A. (2000). Food anaphylaxis. Br Med Bull, 56(4), 925-935.

Sampson, H. A. (2013). Peanut oral immunotherapy: is it ready for clinical practice? J Allergy Clin Immunol Pract, 1(1), 15-21.

Schwartz, R. H. (1992). Allergy, intolerance, and other adverse reactions to foods. Pediatr Ann, 21(10), 654-655, 660-652, 665-674.

Shah, E., Pongracic, J. (2008). Food-induced anaphylaxis: who, what, why, and where? Pediatr Ann, 37(8), 536-541.

Shimamoto, S. R., Bock, S. A. (2002). Update on the clinical features of food-induced anaphylaxis. Curr Opin Allergy Clin Immunol, 2(3), 211-216.

Sicherer, S. H. (2002). Clinical update on peanut allergy. Ann Allergy Asthma Immunol, 88(4), 350-361; quiz 361-352, 394.

Sicherer, S. H., Sampson, H. A. (2010). Food allergy. J Allergy Clin Immunol, 125(2 Suppl 2), S116-125.

Sicherer, S. H., Sampson, H. A. (2014). Food allergy: Epidemiology, pathogenesis, diagnosis, and treatment. J Allergy Clin Immunol, 133(2), 291-307; quiz 308

Sicherer, S.H., Muñoz-Furlong, A., Godbold, J.H., Sampson, H.A. US prevalence of self-reported peanut, tree nut, and sesame allergy: 11-year follow-up. J Allergy Clin Immunol 2010;125(6):1322-6.

Sicherer, S. H., Leung, D. Y. (2005). Advances in allergic skin disease, anaphylaxis, and hypersensitivity reactions to foods, drugs, and insects. J Allergy Clin Immunol, 116(1), 153-163.

Sicherer, S. H., Leung, D. Y. (2009). Advances in allergic skin disease, anaphylaxis, and hypersensitivity reactions to foods, drugs, and insects in 2008. J Allergy Clin Immunol, 123(2), 319-327.

Sicherer, S. H., Leung, D. Y. (2011). Advances in allergic skin disease, anaphylaxis, and hypersensitivity reactions to foods, drugs, and insects in 2010. J Allergy Clin Immunol, 127(2), 326-335.

Sicherer, S. H., Sampson, H. A. (2000). Peanut and tree nut allergy. Curr Opin Pediatr, 12(6), 567-573.

Skripak, J. M., Wood, R. A. (2008). Peanut and tree nut allergy in childhood. Pediatr Allergy Immunol, 19(4), 368-373.

Speer, F. (1976). Food allergy: the 10 common offenders. Am Fam Physician, 13(2), 106-112.

Stahl, M. C., Rans, T. S. (2011). Potential therapies for peanut allergy. Ann Allergy Asthma Immunol, 106(3), 179-187; quiz 188.

Teuber, S. S., Comstock, S. S. Sathe, S. K. Roux, K. H. (2003). Tree nut allergy. Curr Allergy Asthma Rep, 3(1), 54-61.

Thompson, R. L., Miles, L. M., Lunn, J., Devereux, G., Dearman, R. J., Strid, J., Buttriss, J. L. (2010). Peanut sensitisation and allergy: influence of early life exposure to peanuts. Br J Nutr, 103(9), 1278-1286.

Tibbott, R., Clark, A. (2014). Diagnosing and managing peanut allergy in children. Practitioner, 258(1772), 21-24, 22-23.

Vazquez-Ortiz, M., Turner, P. J. (2015). Improving the safety of oral immunotherapy for food allergy. Pediatr Allergy Immunol.

Verma, A. K., Kumar, S. Das, M. Dwivedi, P. D. (2013). A comprehensive review of legume allergy. Clin Rev Allergy Immunol, 45(1), 30-46.

Versluis, A., Knulst, A., C. Kruizinga, A. G., Michelsen, A. Houben, G. F. Baumert, J. L. van Os-Medendorp, H. (2015). Frequency, severity and causes of unexpected allergic reactions to food: a systematic literature review. Clin Exp Allergy, 45(2), 347-367.

Wang, M., Gelfand, E. W. (2014). Targeting Pim1 kinase in the treatment of peanut allergy. Expert Opin Ther Targets, 18(2), 177-183.

Wild, L. G., Lehrer, S. B. (2001). Immunotherapy for food allergy. Curr Allergy Rep, 1(1), 48-53.

Yang, Y. H., Chiang, B. L. (2014). Novel approaches to food allergy. Clin Rev Allergy Immunol, 46(3), 250-257.

Young, M. C. (2015). Taking the leap earlier: the timing of tolerance. Curr Opin Pediatr, 27(6), 736-740.

Yun, J., Katelaris, C. H. (2009). Food allergy in adolescents and adults. Intern Med J, 39(7), 475-478.

Zeiger, R. S. (2000). Dietary aspects of food allergy prevention in infants and children. J Pediatr Gastroenterol Nutr, 30 Suppl, S77-86.

Professional guidelines:

Fiocchi, A., Assa'ad, A. Bahna, S. (2006). Food allergy and the introduction of solid foods to infants: a consensus document. Adverse Reactions to Foods Committee, American College of Allergy, Asthma and Immunology. Ann Allergy Asthma Immunol, 97(1), 10-20; quiz 21, 77.

Fleischer, D. M., Sicherer, S. Greenhawt, M. Campbell, D. Chan, E. Muraro, A. Halken, S. Katz, Y. Ebisawa, M. Eichenfield, L. Sampson, H. Lack, G. Du Toit, G. Roberts, G. Bahnson, H. Feeney, M. Hourihane, J. Spergel, J. Young, M. As'aad, A. Allen, K. Prescott, S. Kapur, S. Saito, H. Agache, I. Akdis, C. A. Arshad, H. Beyer, K. Dubois, A. Eigenmann, P. Fernandez-Rivas, M. Grimshaw, K. Hoffman-Sommergruber, K. Host, A. Lau, S. O'Mahony, L. Mills, C. Papadopoulos, N. Venter, C. Agmon-Levin, N. Kessel, A. Antaya, R. Drolet, B. Rosenwasser, L. (2015). Consensus Communication on Early Peanut Introduction and the Prevention of Peanut Allergy in High-risk Infants. Pediatrics, 136 (3) 600-604.

Fleischer, D. M., Sicherer, S. Greenhawt, M. Campbell, D. Chan, E. Muraro, A. Halken, S. Katz, Y. Ebisawa, M. Eichenfield, L. Sampson, H. Lack, G. Du Toit, G. Roberts, G. Bahnson, H. Feeney, M. Hourihane, J. Spergel, J. Young, M. As'aad, A. Allen, K. Prescott, S. Kapur, S. Saito, H. Agache, I. Akdis, C. A. Arshad, H. Beyer, K. Dubois, A. Eigenmann, P. Fernandez-Rivas, M. Grimshaw, K. Hoffman-Sommergruber, K. Host, A. Lau, S. O'Mahony, L. Mills, C. Papadopoulos, N. Venter, C. Agmon-Levin, N. Kessel, A. Antaya, R. Drolet, B. Rosenwasser, L. (2016). Consensus Communication on Early Peanut Introduction and Prevention of Peanut Allergy in High-Risk Infants. Pediatr Dermatol, 33(1), 103-106.

Hauk, L. (2016). Early Peanut Introduction and Prevention of Peanut Allergy in High-Risk Infants: Consensus Communication. Am Fam Physician, 93(1), 61-62.

Risk assessment:

Rimbaud, L., Heraud, F., La Vieille, S., Leblanc, J. C., Crepet, A. (2010). Quantitative risk assessment relating to adventitious presence of allergens in food: a probabilistic model applied to peanut in chocolate. Risk Anal, 30(1), 7-19.

Comments or editorials:

Allen, K. J., Koplin, J. J. (2015). High consumption of peanuts or tree nuts by non-allergic mothers around the time of pregnancy reduces the risk of nut allergy in the child. Evid Based Nurs, 18(2), 45.

Allen, K. J., Koplin, J. J. (2016). Does LEAP change the screening paradigm for food allergy in infants with eczema? Clin Exp Allergy, 46(1), 42-47.

Brown, H. M. (2007). Would oral desensitization for peanut allergy be safer than avoidance? Ann Allergy Asthma Immunol, 98(2), 203.

Douglas, R. G., O'Hehrir, R. E. (1997). Peanut allergy. Med J Aust, 166(2), 63-64.

Filho, N. R. (2015). [Early introduction of food to prevent food allergy. The LEAP study (Learning Early about Peanut)]. Rev Paul Pediatr, 33(4), 493-494.

Galvin, A. D., Hourihane, J. O., Roberts, S. (2008). Causal pathway analysis of mothers' responses to government advice on peanut avoidance. J Public Health (Oxf), 30(1), 114-115.

Kelso, J. M. (2016). How to apply the LEAP study. J Allergy Clin Immunol, 137(1), 332-334.

Mansfield, L. E. (2013). Oral immunotherapy for peanut allergy in clinical practice is ready. Allergy Asthma Proc, 34(3), 205-209.

Munoz-Furlong, A. (2004). Patient's perspective and public policy regarding anaphylaxis. Novartis Found Symp, 257, 265-274; discussion 274-265, 276-285.

Munoz-Furlong, A.,Weiss, C. C. (2009). Characteristics of food-allergic patients placing them at risk for a fatal anaphylactic episode. Curr Allergy Asthma Rep, 9(1), 57-63.

Rabinovitch, N., Shah, D., Lanser, B. J. (2015). Look before you LEAP: Risk of anaphylaxis in high-risk infants with early introduction of peanut. J Allergy Clin Immunol, 136(3), 822.

Sampson, H. A., Lack, G., Du Toit, G. (2015). Reply: To PMID 25705822. J Allergy Clin Immunol, 136(3), 822-823.

Sicherer, S. H. (2015). Early introduction of peanut to infants at high allergic risk can reduce peanut allergy at age 5 years. Evid Based Med, 20(6), 204.

Sicherer, S. H., Bock, S. A., Zeiger, R. S. (2015). Implications of the "Consensus Communication on Early Peanut Introduction in the Prevention of Peanut Allergy in High-Risk Infants" for Allergists, Primary Care Physicians, Patients, and Society. J Allergy Clin Immunol Pract, 3(5), 649-651.

Symon, B., Crichton, G. (2015). Urgent information on peanut allergy: New evidence from the LEAP study. Aust Fam Physician, 44(9), 618.

Taylor, S. L., Bush, R. K., Busse, W. W. (1986). Avoidance diets--how selective should we be? N Engl Reg Allergy Proc, 7(6), 527-532.

Wennergren, G. (2009). What if it is the other way around? Early introduction of peanut and fish seems to be better than avoidance. Acta Paediatr, 98(7), 1085-1087.

Abstracts written in English for articles written in a foreign language:

Baranes, T., Bidat, E. (2008). [Food hypersensibility: inhalation reactions are different from ingestion reactions]. Arch Pediatr, 15(6), 1091-1094.

Brand, P. L. (2007). [Anaphylaxis: facts and fallacies]. Ned Tijdschr Geneeskd, 151(10), 574-577.

Chouraqui, J. P., Dupont, C., Bocquet, A., Bresson, J. L., Briend, A., Darmaun, D., Frelut, M. L., Ghisolfi, J., Girardet, J. P., Goulet, O., Putet, G., Rieu, D., Rigo, J., Turck, D., Vidailhet, M. (2008). [Feeding during the first months of life and prevention of allergy]. Arch Pediatr, 15(4), 431-442.

Feuillet-Dassonval, C., Agne, P. S., Rance, F., Bidat, E. (2006). [What type of avoidance for peanut allergic children?]. Arch Pediatr, 13(9), 1245-1251.

Fremont, S., Morisset, M., Gerard, P., Nicolas, J. P., Moneret-Vautrin, D. A. (1999). [Measurement of levels of specific IgE by the Efficient New Enzymatic Allergy (ENEA) System II (CIS bio)]. Allerg Immunol (Paris), 31(8), 278-284.

Hogendijk, S., Eigenmann, P. A., Hauser, C. (1998). [The problem of hidden food allergens: two cases of anaphylaxis to peanut proteins concealed in a pizza sauce]. Schweiz Med Wochenschr, 128(29-30), 1134-1137.

Kawaguchi, T., Futamara, M., Kitazawa, H., Ohya, Y. (2015). [Rationale for eliminating certain foods in children with food allergy.]. Arerugi, 64(5), 714-720.

Kolacek, S. (2011). [Food hypersensitivity in children]. Acta Med Croatica, 65(2), 155-161.

Kukkonen, A. K., Makela, M., Pelkonen, A. (2013). [Nut allergy - a difficult problem for the clinician]. Duodecim, 129(12), 1263-1270.

Pajno, G. B., Passalacqua, G., La Grutta, S., Vita, D., Feliciotto, R., Parmiani, S., Barberio, G. (2002). True multifood allergy in a 4-year-old child: a case study. Allergol Immunopathol (Madr), 30(6), 338-341.

Rance, F. (2000). [Current childhood food allergies]. Allerg Immunol (Paris), 32(10), 366-376.

Szepfalusi, Z. (2012). [Food allergy in childhood]. Wien Med Wochenschr, 162(23-24), 525-532.

Szepfalusi, Z., Spiesz, K., Huttegger, I. (2015). [Diagnostics and management of food allergies in childhood and adolescence]. Wien Med Wochenschr, 165(17-18), 354-360.
Turcanu, V. (2010). [Peanut allergy]. Pneumologia, 59(2), 77-82.

Zhai, J. X., Zhang, Z. X., Feng, Y. J., Ding, S. S. (2010). [Effect of exposure to higher decabrominated diphenyl ether (PBDE-209) on learning and memory functions of BALB/c mice]. Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi, 28(1), 25-29.

In vitro studies:

Barre, A., Sordet, C., Culerrier, R., Rance, F., Didier, A., Rouge, P. (2008). Vicilin allergens of peanut and tree nuts (walnut, hazelnut and cashew nut) share structurally related IgE-binding epitopes. Mol Immunol, 45(5), 1231-1240.

Cocco, R. R., Jarvinen, K. M., Sampson, H. A., Beyer, K. (2003). Mutational analysis of major, sequential IgE-binding epitopes in alpha s1-casein, a major cow's milk allergen. J Allergy Clin Immunol, 112(2), 433-437.

Diaz-Ruiz, J. R., Kaper, J. M. (1978). Isolation of viral double-stranded RNAs using a LiCl fractionation procedure. Prep Biochem, 8(1), 1-17.

Hebling, C. M., Ross, M. M., Callahan, J. H., McFarland, M. A. (2012). Size-selective fractionation and visual mapping of allergen protein chemistry in Arachis hypogaea. J Proteome Res, 11(11), 5384-5395.

Hemming, F. J., Saxod, R. (1997). Keratan sulphate is present in developing chick skin in vivo where it could constitute a barrier to advancing neurites as observed in vitro. J Neurosci Res, 48(2), 133-145.

Hotary, K. B., Tosney, K. W. (1996). Cellular interactions that guide sensory and motor neurites identified in an embryo slice preparation. Dev Biol, 176(1), 22-35.

Jacobs, J. L., Carroll, T. L., Sundin, G. W. (2005). The role of pigmentation, ultraviolet radiation tolerance, and leaf colonization strategies in the epiphytic survival of phyllosphere bacteria. Microb Ecol, 49(1), 104-113.

Kiening, M., Niessner, R., Drs, E., Baumgartner, S., Krska, R., Bremer, M., Tomkies, V., Reece, P., Danks, C., Immer, U., Weller, M. G. (2005). Sandwich immunoassays for the determination of peanut and hazelnut traces in foods. J Agric Food Chem, 53(9), 3321-3327.

Knoll, J. E., Ramos, M. L., Zeng, Y., Holbrook, C. C., Chow, M., Chen, S., Maleki, S., Bhattacharya, A., Ozias-Akins, P. (2011). TILLING for allergen reduction and improvement of quality traits in peanut (Arachis hypogaea L.). BMC Plant Biol, 11, 81.

Krzystyniak, K., Desjardins, R., Therien, H. M., Banska, W., Tancrede, P., Descotes, J. (1994). Lymphocyte activation by liposome-trapped streptozotocin in murine popliteal lymph node (PLN) test. Int J Immunopharmacol, 16(10), 817-824.

Pascal, M., Konstantinou, G. N., Masilamani, M., Lieberman, J., Sampson, H. A. (2013). In silico prediction of Ara h 2 T cell epitopes in peanut-allergic children. Clin Exp Allergy, 43(1), 116-127.

Ramos, M. L., Huntley, J. J., Maleki, S. J., Ozias-Akins, P. (2009). Identification and characterization of a hypoallergenic ortholog of Ara h 2.01. Plant Mol Biol, 69(3), 325-335.

Schmitt, D. A., Cheng, H., Maleki, S. J., Burks, A. W. (2004). Competitive inhibition ELISA for quantification of Ara h 1 and Ara h 2, the major allergens of peanuts. J AOAC Int, 87(6), 1492-1497.

Sundin, G. W., Jacobs, J. L. (1999). Ultraviolet Radiation (UVR) Sensitivity Analysis and UVR Survival Strategies of a Bacterial Community from the Phyllosphere of Field-Grown Peanut (Arachis hypogeae L.). Microb Ecol, 38(1), 27-38.

Tran, D. T,. Knez, K., Janssen, K. P., Pollet, J., Spasic, D., Lammertyn, J. (2013). Selection of aptamers against Ara h 1 protein for FO-SPR biosensing of peanut allergens in food matrices. Biosens Bioelectron, 43, 245-251.

Yeung, J. M., Collins, P. G. (1996). Enzyme immunoassay for determination of peanut proteins in food products. J AOAC Int, 79(6), 1411-1416.

Animal studies:

Benoit, S. C., Morell, J. R. Davidson, T. L. (1999). Lesions of the amygdala central nucleus abolish lipoprivic-enhanced responding during oil-predicting conditioned stimuli. Behav Neurosci, 113(6), 1233-1241.

Borlongan, C. V., Sumaya, I. C., Moss, D. E. (2005). Methanesulfonyl fluoride, an acetylcholinesterase inhibitor, attenuates simple learning and memory deficits in ischemic rats. Brain Res, 1038(1), 50-58.

Davidson, T. L., Altizer, A. M., Benoit, S. C., Walls, E. K., Powley, T. L. (1997). Encoding and selective activation of “metabolic memories” in the rat. Behav Neurosci, 111(5), 1014-1030.

George, G., Mellanby, J. (1974). A further study on the effect of physostigmine on memory in rats. Brain Res, 81(1), 133-144.

Hidalgo, A., Burgos, V., Viola, H., Medina, J., Argibay, P. (2006). Differential expression of glycans in the hippocampus of rats trained on an inhibitory learning paradigm. Neuropathology, 26(6), 501-507.

Li, X. M., Serebrisky, D., Lee, S. Y., Huang, C. K., Bardina, L., Schofield, B. H., Stanley, J. S., Burks, A. W., Bannon, G. A., Sampson, H. A. (2000). A murine model of peanut anaphylaxis: T- and B-cell responses to a major peanut allergen mimic human responses. J Allergy Clin Immunol, 106(1 Pt 1), 150-158.

Neill, M., Dixon, P. S. (2007). Effects of a preincisional 14-day course of valerian on natural killer cell activity in Sprague-Dawley male rats undergoing abdominal surgery. Holist Nurs Pract, 21(4), 187-193.

Oakley, R. A., Lasky, C. J., Erickson, C. A., Tosney, K. W. (1994). Glycoconjugates mark a transient barrier to neural crest migration in the chicken embryo. Development, 120(1), 103-114.

Olthof, A., Iden, C. M., Roberts, W. A. (1997). Judgements of ordinality and summation of number symbols by squirrel monkeys (Saimiri sciureus). J Exp Psychol Anim Behav Process, 23(3), 325-339.

Schiessl, B., Zenmann, B., Hodgin-Pickart, L. A., de Weck, A. L., Griot-Wenk, M., Mayer, P., Nefzger, M., Schneider, H., Liehl, E. (2003). Importance of early allergen contact for the development of a sustained immunoglobulin E response in a dog model. Int Arch Allergy Immunol, 130(2), 125-134.

Xu, X., Liu, X., Zhang, Q., Zhang, G., Lu, Y., Ruan, Q., Dong, F., Yang, Y. (2013). Sex-specific effects of bisphenol-A on memory and synaptic structural modification in hippocampus of adult mice. Horm Behav, 63(5), 766-775.

Newspaper article:

Schoofs, M. (1998). The Norvir switch. J Int Assoc Physicians AIDS Care, 4(9), 64-68.

Articles describing studies that did not measure peanut intake and/or peanut allergy in the study subjects:

Avery, N. J., King, R. M., Knight, S., & Hourihane, J. O. (2003). Assessment of quality of life in children with peanut allergy. Pediatr Allergy Immunol, 14(5), 378-382.

Barnett, J., Botting, N., Gowland, M. H., & Lucas, J. S. (2012). The strategies that peanut and nut-allergic consumers employ to remain safe when travelling abroad. Clin Transl Allergy, 2(1), 12.

Bellou, A., Kanny, G., Fremont, S., & Moneret-Vautrin, D. A. (1997). Transfer of atopy following bone marrow transplantation. Ann Allergy Asthma Immunol, 78(5), 513-516.

Binkley, K. E., Leaver, C., & Ray, J. G. (2011). Antenatal risk factors for peanut allergy in children. Allergy Asthma Clin Immunol, 7, 17.

Bishop, J. M., Hill, D. J., & Hosking, C. S. (1990). Natural history of cow milk allergy: clinical outcome. J Pediatr, 116(6), 862-867.

Brennecke, S., Becker, W. M., Lepp, U., & Jappe, U. (2007). Anaphylactic reaction to lupine flour. J Dtsch Dermatol Ges, 5(9), 774-776.

Crespo, J. F., Rodriguez, J., James, J. M., Daroca, P., Reano, M., & Vives, R. (2002). Reactivity to potential cross-reactive foods in fruit-allergic patients: implications for prescribing food avoidance. Allergy, 57(10), 946-949.

Dean, T., Venter, C., Pereira, B., Grundy, J., Clayton, C. B., & Higgins, B. (2007). Government advice on peanut avoidance during pregnancy--is it followed correctly and what is the impact on sensitization? J Hum Nutr Diet, 20(2), 95-99.

Derby, C. J., Gowland, M. H., & Hourihane, J. O. (2005). Sesame allergy in Britain: a questionnaire survey of members of the Anaphylaxis Campaign. Pediatr Allergy Immunol, 16(2), 171-175.

Eigenmann, P. A., Caubet, J. C., & Zamora, S. A. (2006). Continuing food-avoidance diets after negative food challenges. Pediatr Allergy Immunol, 17(8), 601-605.

Erwin, E. A., James, H. R., Gutekunst, H. M., Russo, J. M., Kelleher, K. J., & Platts-Mills, T. A. (2010). Serum IgE measurement and detection of food allergy in pediatric patients with eosinophilic esophagitis. Ann Allergy Asthma Immunol, 104(6), 496-502.

Ewan, P. W., & Clark, A. T. (2001). Long-term prospective observational study of patients with peanut and nut allergy after participation in a management plan. Lancet, 357(9250), 111-115.

Ewan, P. W., & Clark, A. T. (2005). Efficacy of a management plan based on severity assessment in longitudinal and case-controlled studies of 747 children with nut allergy: proposal for good practice. Clin Exp Allergy, 35(6), 751-756.

Field, E. A., Longman, L. P., al-Sharkawi, M., & King, C. M. (1997). An immediate (type I) hypersensitivity reaction during placement of a dental rubber dam. Eur J Prosthodont Restor Dent, 5(2), 75-78.

Gerrard, J. W., & Perelmutter, L. (1986). IgE-mediated allergy to peanut, cow's milk, and egg in children with special reference to maternal diet. Ann Allergy, 56(4), 351-354.

Guinnepain, M. T., Eloit, C., Raffard, M., Brunet-Moret, M. J., Rassemont, R., & Laurent, J. (1996). Exercise-induced anaphylaxis: useful screening of food sensitization. Ann Allergy Asthma Immunol, 77(6), 491-496.

Gunnarsson, N., Marklund, B., Ahlstedt, S., Borell, L., & Nordstrom, G. (2005). Allergy-like conditions and health-care contacts among children with exclusion diets at school. Scand J Caring Sci, 19(1), 46-52.

Hon, K. L., Leung, T. F., Ching, G., Chow, C. M., Luk, V., Ko, W. S., & Ng, P. C. (2008). Patterns of food and aeroallergen sensitization in childhood eczema. Acta Paediatr, 97(12), 1734-1737.

Horwitz, A. A., Hossain, J., & Yousef, E. (2009). Correlates of outcome for atopic dermatitis. Ann Allergy Asthma Immunol, 103(2), 146-151.

Hourihane, J. O., Aiken, R., Briggs, R., Gudgeon, L. A., Grimshaw, K. E., DunnGalvin, A., & Roberts, S. R. (2007). The impact of government advice to pregnant mothers regarding peanut avoidance on the prevalence of peanut allergy in United Kingdom children at school entry. J Allergy Clin Immunol, 119(5), 1197-1202.

Hourihane, J. O., Kilburn, S. A., Dean, P., & Warner, J. O. (1997). Clinical characteristics of peanut allergy. Clin Exp Allergy, 27(6), 634-639.

Hourihane, J. O., Rhodes, H. L., Jones, A. M., Veys, P., & Connett, G. J. (2005). Resolution of peanut allergy following bone marrow transplantation for primary immunodeficiency. Allergy, 60(4), 536-537.

Hsu, M. L., & Li, L. F. (2012). Prevalence of food avoidance and food allergy in Chinese patients with chronic urticaria. Br J Dermatol, 166(4), 747-752.

Khoo, J., Shek, L. P., Khor, E. S., Wang, D. Y., & Lee, B. W. (2001). Pattern of sensitization to common environmental allergens amongst atopic Singapore children in the first 3 years of life. Asian Pac J Allergy Immunol, 19(4), 225-229.

Klein, R. L., Novak, R. W., & Novak, P. E. (1986). T-cryptantigen exposure in neonatal necrotizing enterocolitis. J Pediatr Surg, 21(12), 1155-1158.

Lavine, E., Clarke, A., Joseph, L., Shand, G., Alizadehfar, R., Asai, Y., Ben-Shoshan, M. (2015). Peanut avoidance and peanut allergy diagnosis in siblings of peanut allergic children. Clin Exp Allergy, 45(1), 249-254.

Leftwich, J., Barnett, J., Muncer, K., Shepherd, R., Raats, M. M., Hazel Gowland, M., & Lucas, J. S. (2011). The challenges for nut-allergic consumers of eating out. Clin Exp Allergy, 41(2), 243-249.

Leitch, I. S., Walker, M. J., & Davey, R. (2005). Food allergy: gambling your life on a take-away meal. Int J Environ Health Res, 15(2), 79-87.

Leung, T. F., Yung, E., Wong, Y. S., Li, C. Y., & Wong, G. W. (2009). Quality-of-life assessment in Chinese families with food-allergic children. Clin Exp Allergy, 39(6), 890-896.

Lindvik, H., Holden, L., Lovik, M., Cvancarova, M., & Halvorsen, R. (2008). Lupin sensitization and clinical allergy in food allergic children in Norway. Acta Paediatr, 97(1), 91-95.

Loesche, W. J., Bromberg, J., Terpenning, M. S., Bretz, W. A., Dominguez, B. L., Grossman, N. S., & Langmore, S. E. (1995). Xerostomia, xerogenic medications and food avoidances in selected geriatric groups. J Am Geriatr Soc, 43(4), 401-407.

Ma, S., Sicherer, S. H., & Nowak-Wegrzyn, A. (2003). A survey on the management of pollen-food allergy syndrome in allergy practices. J Allergy Clin Immunol, 112(4), 784-788.

Maloney, J. M., Chapman, M. D., & Sicherer, S. H. (2006). Peanut allergen exposure through saliva: assessment and interventions to reduce exposure. J Allergy Clin Immunol, 118(3), 719-724.

Meglio, P., Giampietro, P. G., Gabriele, I., Carello, R., Avitabile, S., & Galli, E. (2011). Oral desensitisation with food is food-specific and protein-specific. Int J Immunopathol Pharmacol, 24(3), 803-811.

Mihrshahi, S., Webb, K., Almqvist, C., & Kemp, A. S. (2008). Adherence to allergy prevention recommendations in children with a family history of asthma. Pediatr Allergy Immunol, 19(4), 355-362.

National Research Council (NRC). 2011. Reference Manual on Scientific Evidence: Third Edition. The National Academies Press, Washington, DC, page 220.

Olatinwo, R. O., Paz, J. O., Brown, S. L., Kemerait, R. C., Culbreath, A. K., Beasley, J. P., & Hoogenboom, G. (2008). A predictive model for spotted wilt epidemics in peanut based on local weather conditions and the tomato spotted wilt virus risk index. Phytopathology, 98(10), 1066-1074.

Oliver, E. M., Grimshaw, K. E., Schoemaker, A. A., Keil, T., McBride, D., Sprikkelman, A. B., Roberts, G. (2014). Dietary habits and supplement use in relation to national pregnancy recommendations: data from the EuroPrevall birth cohort. Matern Child Health J, 18(10), 2408-2425.

Phan, T. G., Strasser, S. I., Koorey, D., McCaughan, G. W., Rimmer, J., Dunckley, H., Adelstein, S. (2003). Passive transfer of nut allergy after liver transplantation. Arch Intern Med, 163(2), 237-239.

Rhim, G. S., & McMorris, M. S. (2001). School readiness for children with food allergies. Ann Allergy Asthma Immunol, 86(2), 172-176.

Romano, A., Di Fonso, M., Giuffreda, F., Papa, G., Artesani, M. C., Viola, M., Zeppilli, P. (2001). Food-dependent exercise-induced anaphylaxis: clinical and laboratory findings in 54 subjects. Int Arch Allergy Immunol, 125(3), 264-272.

Rose, S., Weld-Moore, R., Ghazali, N., & Newman, L. (2011). 'I've got hay-fever and my mouth is stinging!' Br Dent J, 211(8), 369-370.

Rowe, J., Kusel, M., Holt, B. J., Suriyaarachchi, D., Serralha, M., Hollams, E., Holt, P. G. (2007). Prenatal versus postnatal sensitization to environmental allergens in a high-risk birth cohort. J Allergy Clin Immunol, 119(5), 1164-1173.

Sergeant, P., Kanny, G., Morisset, M., Waguet, J. C., Bastien, C., & Moneret-Vautrin, D. A. (2003). Food safety of allergic patients in hospitals: implementation of a quality strategy to ensure correct management. Eur Ann Allergy Clin Immunol, 35(4), 120-123.

Sicherer, S. H., Burks, A. W., & Sampson, H. A. (1998). Clinical features of acute allergic reactions to peanut and tree nuts in children. Pediatrics, 102(1), e6.

Simons, E., Weiss, C. C., Furlong, T. J., & Sicherer, S. H. (2005). Impact of ingredient labeling practices on food allergic consumers. Ann Allergy Asthma Immunol, 95(5), 426-428.

Steinman, H. A., & Potter, P. C. (1994). The precipitation of symptoms by common foods in children with atopic dermatitis. Allergy Proc, 15(4), 203-210.

Trendelenburg, V., Rohrbach, A., Schulz, G., Schwarz, V., & Beyer, K. (2014). Molecular sIgE profile in infants and young children with peanut sensitization and eczema. Allergo J Int, 23(5), 152-157.

Turke, J., Venter, C., & Dean, T. (2005). Maternal experiences of peanut avoidance during pregnancy/lactation: an in-depth qualitative study. Pediatr Allergy Immunol, 16(6), 512-518.

van Odijk, J., Hulthen, L., Ahlstedt, S., & Borres, M. P. (2004). Introduction of food during the infant's first year: a study with emphasis on introduction of gluten and of egg, fish and peanut in allergy-risk families. Acta Paediatr, 93(4), 464-470.

Wassenberg, J., & Hofer, M. (2007). Lupine-induced anaphylaxis in a child without known food allergy. Ann Allergy Asthma Immunol, 98(6), 589-590.

Weiss, C., Munoz-Furlong, A., Furlong, T. J., & Arbit, J. (2004). Impact of food allergies on school nursing practice. J Sch Nurs, 20(5), 268-278.

Yu, J. W., Kagan, R., Verreault, N., Nicolas, N., Joseph, L., St Pierre, Y., & Clarke, A. (2006). Accidental ingestions in children with peanut allergy. J Allergy Clin Immunol, 118(2), 466-472.

Chandra, R. K., Puri, S., Suraiya, C., Cheema, P. S. (1986). Influence of maternal food antigen avoidance during pregnancy and lactation on incidence of atopic eczema in infants. Clin Allergy, 16(6), 563-569.

Factor, J. M., Mendelson, L., Lee, J., Nouman, G., Lester, M. R. (2012). Effect of oral immunotherapy to peanut on food-specific quality of life. Ann Allergy Asthma Immunol, 109(5), 348-352 e342.

Ferdman, R. M., Church, J. A. (2006). Mixed-up nuts: identification of peanuts and tree nuts by children. Ann Allergy Asthma Immunol, 97(1), 73-77.

Hostetler, T. L., Hostetler, S. G., Phillips, G., Martin, B. L. (2012). The ability of adults and children to visually identify peanuts and tree nuts. Ann Allergy Asthma Immunol, 108(1), 25-29.

Kao, L., Bhangoo, P. S., Roy, L., Bird, J. A. (2013). Identification of peanuts and tree nuts: are allergists smarter than their patients? Ann Allergy Asthma Immunol, 111(4), 282-285.

Kasera, R., Singh, A. B., Lavasa, S., Prasad, K. N., Arora, N. (2015). Enzymatic hydrolysis: a method in alleviating legume allergenicity. Food Chem Toxicol, 76, 54-60.

Kawano, F., Nagao, K., Inoue, S., Matsumoto, N. (1996). Influence of the buccolingual position of artificial posterior teeth on the pressure distribution on the supporting tissue under a complete denture. J Oral Rehabil, 23(7), 456-463.

Zeiger, R. S., Heller, S., Mellon, M. H., Forsythe, A. B., O'Connor, R. D., Hamburger, R. N., Schatz, M. (1989). Effect of combined maternal and infant food-allergen avoidance on development of atopy in early infancy: a randomized study. J Allergy Clin Immunol, 84(1), 72-89.

Zeiger, R. S., Heller, S. (1995). The development and prediction of atopy in high-risk children: follow-up at age seven years in a prospective randomized study of combined maternal and infant food allergen avoidance. J Allergy Clin Immunol, 95(6), 1179-1190.

Studies that were conducted on diseased populations (already diagnosed with peanut allergy prior to study enrollment):

Anagnostou, K., Islam, S., King, Y., Foley, L., Pasea, L., Bond, S., Palmer, C., Deighton, J., Ewan, P., Clark, A. (2014). Assessing the efficacy of oral immunotherapy for the desensitisation of peanut allergy in children (STOP II): a phase 2 randomised controlled trial. Lancet, 383(9925), 1297-1304.

Anagnostou, K., Islam, S., King, Y., Foley, L., Pasea, L., Palmer, C., Bond, S., Ewan, P., Clark, A. (2014). Study of induction of Tolerance to Oral Peanut: a randomised controlled trial of desensitisation using peanut oral immunotherapy in children (STOP II). In N. I. f. H. Research (Ed.), Efficacy and Mechanism Evaluation (Vol. 1). Southampton UK: Queen's Printer and Controller of HMSO 2014. NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Ball, H., Luyt, D., Bravin, K., & Kirk, K. (2011). Single nut or total nut avoidance in nut allergic children: outcome of nut challenges to guide exclusion diets. Pediatr Allergy Immunol, 22(8), 808-812.

Blumchen, K., Ulbricht, H., Staden, U., Dobberstein, K., Beschorner, J., de Oliveira, L. C., Shreffler, W. G., Sampson, H. A., Niggemann, B., Wahn, U., Beyer, K. (2010). Oral peanut immunotherapy in children with peanut anaphylaxis. J Allergy Clin Immunol, 126(1), 83-91 e81.

Cherkaoui, S., Ben-Shoshan, M., Alizadehfar, R., Asai, Y., Chan, E., Cheuk, S., Clarke, A. (2015). Accidental exposures to peanut in a large cohort of Canadian children with peanut allergy. Clin Transl Allergy, 5, 16.

Deschildre, A., Elegbede, C. F., Just, J., Bruyere, O., Van der Brempt, X., Papadopoulos, A., Moneret-Vautrin, D. A. (2016). Peanut-allergic patients in the MIRABEL survey: characteristics, allergists' dietary advice and lessons from real life. Clin Exp Allergy, 46(4), 610-620.

Du Toit G, Katz Y, Sasieni P, Mesher D, Maleki SJ, Fisher HR, Fox AT, Turcanu V, Amir T, Zadik-Mnuhin G, Cohen A, Livne I, Lack G. (2008). Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy. J Allergy Clin Immunol. Nov;122(5):984-91.

Michaud, E., Evrard, B., Pereira, B., Rochette, E., Bernard, L,. Rouzaire, P. O., Gourdon-Dubois, N., Merlin, E., Fauquert, J. L. (2015). Peanut oral immunotherapy in adolescents: study protocol for a randomized controlled trial. Trials, 16, 197.

Narisety, S. D., Frischmeyer,G., P. A. Keet, C. A. Gorelik, M. Schroeder, J. Hamilton, R. G. Wood, R. A. (2015). A randomized, double-blind, placebo-controlled pilot study of sublingual versus oral immunotherapy for the treatment of peanut allergy. J Allergy Clin Immunol, 135(5), 1275-1282 e1271-1276.

Nelson, H. S., Lahr, J., Rule, R., Bock, A., Leung, D. (1997). Treatment of anaphylactic sensitivity to peanuts by immunotherapy with injections of aqueous peanut extract. J Allergy Clin Immunol, 99(6 Pt 1), 744-751.

Oppenheimer, J. J., Nelson, H. S., Bock, S. A., Christensen, F., Leung, D. Y. (1992). Treatment of peanut allergy with rush immunotherapy. J Allergy Clin Immunol, 90(2), 256-262.

Wasserman, R. L., Factor, J. M., Baker, J. W., Mansfield, L. E., Katz, Y., Hague, A. R., Elizur, A. (2014). Oral immunotherapy for peanut allergy: multipractice experience with epinephrine-treated reactions. J Allergy Clin Immunol Pract, 2(1), 91-96.